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REVIEW

New Applications of Ninhydrin in the Synthesis of Polyheterocyclic Compounds

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Abstract—The review demonstrates new applications of ninhydrin as a versatile reagent in organic synthesis for the preparation of a wide series of polycyclic compounds containing benzofuran, dihydropyrrole, pyrrole, imidazole, pyrimidine, propellane, and other fragments.

Keywords: ninhydrin, multicomponent reactions, ninhydrin adducts, phenols, amines, enamines, *N*-hydroxyureas, *N*,*N*′-dialkylureas, *N*-alkoxy-*N*′-arylureas, imidazo[1,5-*a*]pyridines

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1. INTRODUCTION

The design and synthesis of various molecular entities with the use of vicinal tricarbonyl compounds constitute a promising field of research in organic and medicinal chemistry [1]. Ninhydrin occupies a particular position among other tricarbonyl compounds due to its low cost, availability, and high reactivity. The presence of three electron-withdrawing carbonyl groups linked to a benzene ring makes the ninhydrin molecule very interesting from the structural viewpoint; therefore, interest in the use of ninhydrin in multicomponent reactions to obtain complex polycyclic system increases. Some of the synthesized compounds showed high biological activity, including antitumor, anti-inflammatory, antibacterial, and antiviral properties.

Numerous reactions of ninhydrin [2–4] leading to the formation of a wide series of carbo- and heterocyclic compounds have been reported. The present review focuses on recent advances in the synthesis of polyheterocyclic compounds via multicomponent reactions with the participation of ninhydrin, as well as by reactions of ninhydrin with 1,3-dicarbonyl compounds, phenols, amines, enamines, *N*-hydroxyureas, *N*,*N*′-dialkylureas, *N*-alkoxy-*N*′-arylureas, imidazo[1,5-*a*]pyridines, and other compounds.

2. SYNTHESIS OF POLYHETEROCYCLIC COMPOUNDS BY MULTICOMPONENT REACTIONS INVOLVING NINHYDRIN

Multicomponent reactions provide an efficient tool for the construction of complex molecules, where ninhydrin plays the role of privileged synthon [5]. These reactions could lead to the formation of heterocycles fused to an indene fragment, nitrogen heterocycles spiro fused to indanone, spiro-indene-pyrans, indeno-

quinoxalines, spiro-indene-quinoxalines, propellane derivatives, and a number of other compounds.

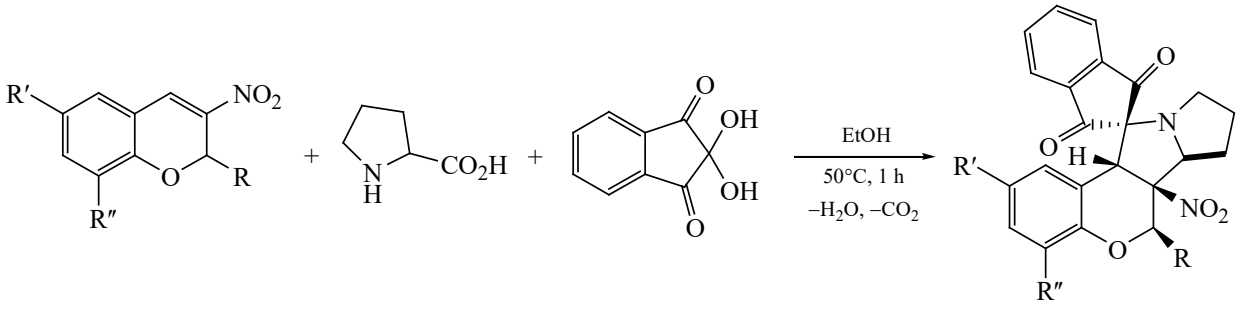
endo-Spiro[chromeno[3,4-*a*]pyrrolizidine-11,2′-indene]-1′,3′-diones **2** were synthesized in high yields by regio- and stereoselective 1,3-dipolar cycloaddition of stabilized azomethine ylides generated in situ from ninhydrin and proline to the nitro group-activated double bond of 3-nitro-2-(trifluoromethyl)- and 3-nitro-2-phenyl-2*H*-chromenes **1** on heating in ethanol [6] (Scheme 1). No regioisomeric adducts were formed due to unfavorable dipole–dipole interaction between the C=O and NO_2 groups in the transition state. Compounds **2** are interesting from the viewpoint of medicinal chemistry.

Fused polycyclic pyrrolines are one of the most important classes of heterocycles; they represent the core fragment of many drugs, such as pemetrexed, moxifloxacin, and zopiclone, which exhibit antitumor, antibacterial, and sedative activities, respectively [7]. Indanone derivatives possess antitumor, antihypertensive, antiallergic, and other properties. Polyhydroxylated indenopyrroles are potent glycosidase inhibitors, DNA intercalators, and estrogenic agents [8].

Rahimi et al. [9] reported a convenient one-pot synthesis of new polysubstituted derivatives of 2-arylaminodihydroxyindenopyrroles **4** by the three-component condensation of ninhydrin, *N*-methyl-1-(methylsulfanyl)-2-nitroethen-1-amine (**3**), and aromatic amines (Scheme 2). The proposed reaction mechanism involved the formation of intermediates **A**–**C**. The procedure is characterized by mild reaction conditions, the use of readily available reagents, the absence of a catalyst, short reaction times, and good yields.

Rezvanian et al. [10] developed a convenient and efficient method for the one-pot synthesis of new indeno[1,2-*b*]furan-3-carboxamides **6** and indeno-[1,2-*b*]pyrrole-3-carboxamides **8** from readily available

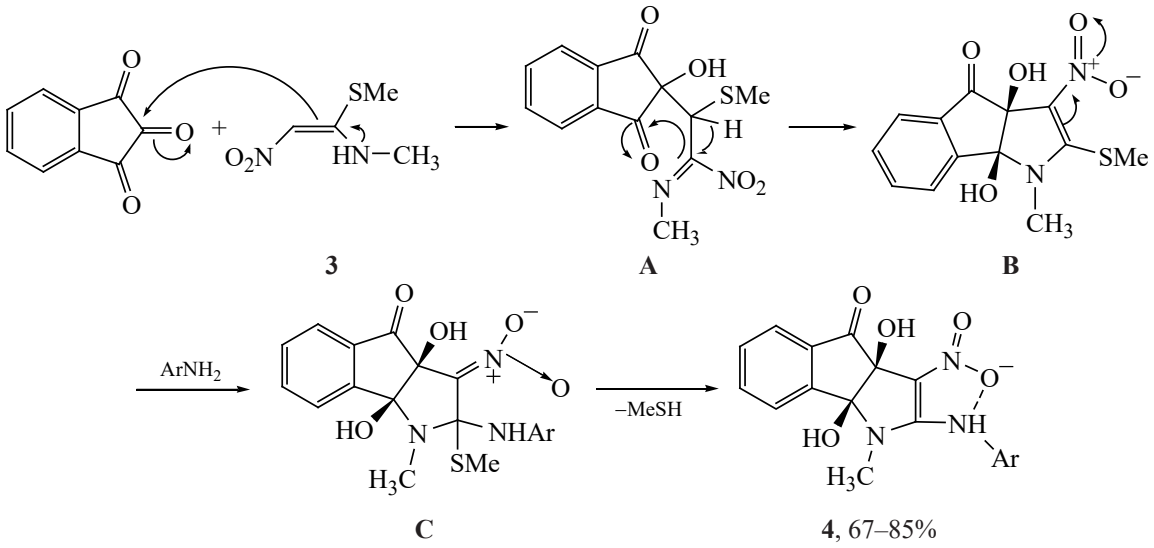
Scheme 1.



1 **2**, 84–90%

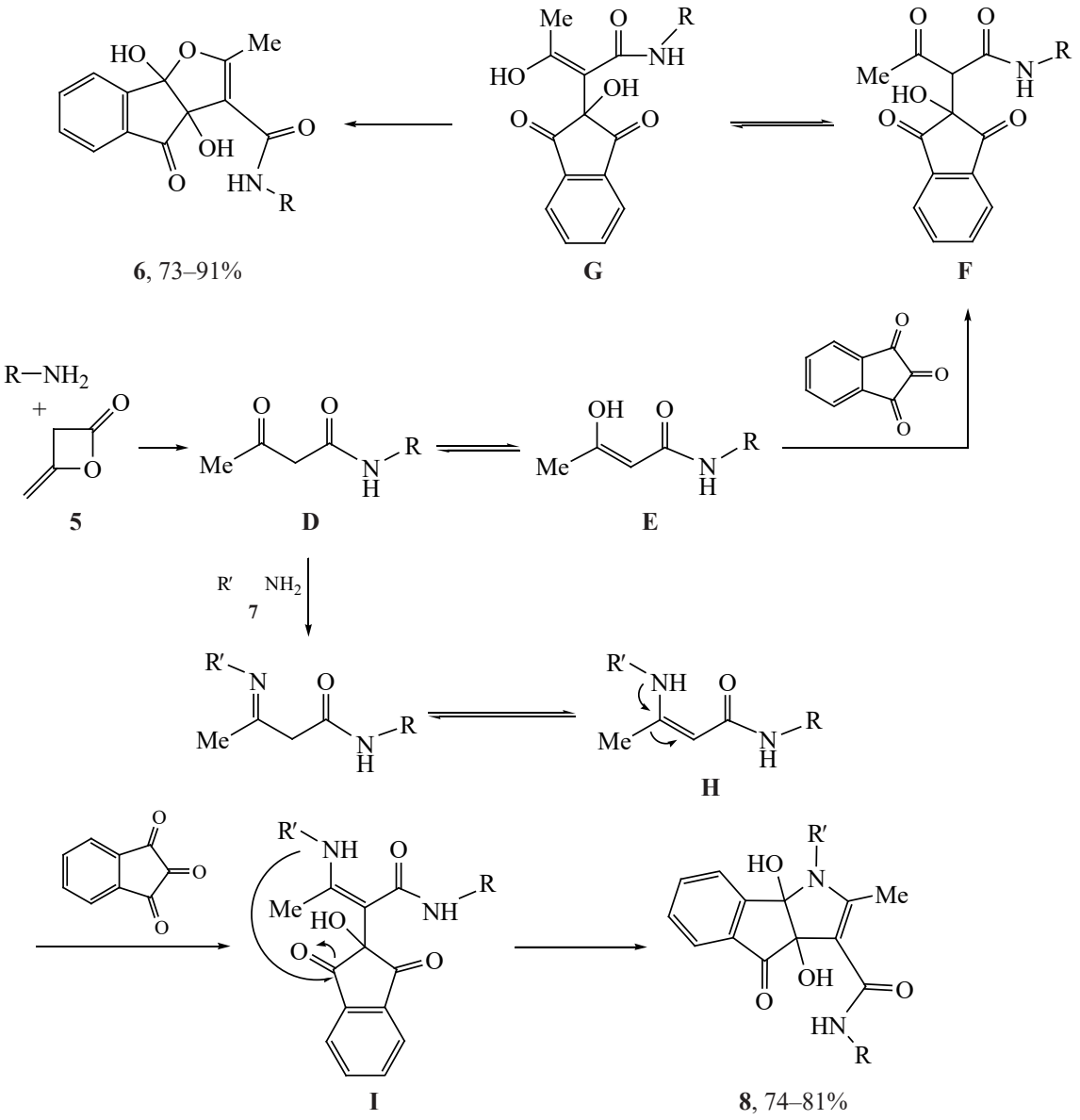
R = CF_3; R′, R″ = H, Me, MeO, EtO, Cl, Br, NO_2.

Scheme 2.



3 **A** **B** **C** **4**, 67–85%

Scheme 3.

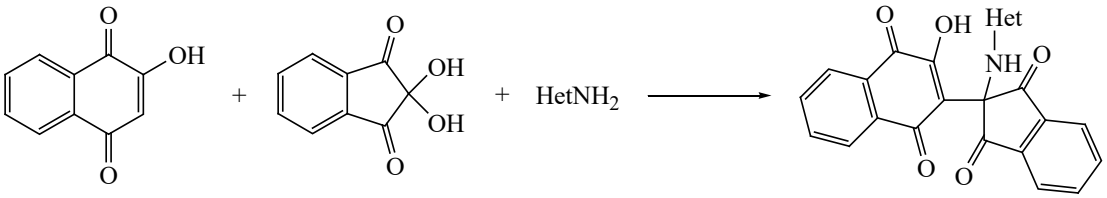


R = *i*-Bu, Et, Bu, *cyclo*-C_5H_9, Bn, Pr; R′ = Pr, Bu, Et, *i*-Bu.

initial compounds. The reactions were carried out under neutral conditions without a catalyst, and a probable reaction mechanism was proposed (Scheme 3). The reaction begins with nucleophilic addition of an amine to 4-methylideneoxetan-2-one (**5**), which is followed by opening of the four-membered ring and hydrogen transfer to form oxobutanamide **D**. The latter occurs in equilibrium with enol **E** which attacks the C^2=O carbonyl group of ninhydrin to give intermediate **F** which undergoes tautomerization to structure **G**, and the subsequent heterocyclization of **G** yields indeno-[1,2-*b*]furan **6**. In the synthesis of indeno[1,2-*b*]pyrroles **8**, intermediate oxobutanamide **D** reacts with another primary amine **7** with the formation of ketone imine which tautomerizes to enamine **H**. The subsequent reaction of **H** with ninhydrin produces intermediate **I** whose cyclization leads to final indeno-[1,2-*b*]pyrrole **8**.

The three-component reaction of ninhydrin, 2-hydroxy-1,4-naphthoquinone, and heteroaromatic amines under solvent-free conditions in the absence of a catalyst at 75°C (10–60 min) afforded 80–87% of 1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)naphthalene-1,4-diones **9a**–**9j** [11] (Scheme 4).

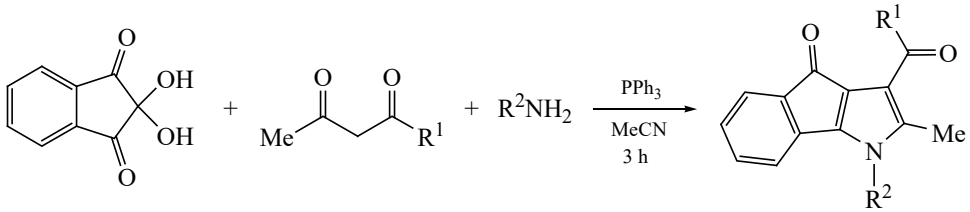
Scheme 4.



9a–9j

Het = 4-methylpyridin-2-yl (**a**), pyridin-2-yl (**b**), 6-methylpyridin-2-yl (**c**), 3-methylpyridin-2-yl (**d**), pyridin-3-yl (**e**), pyridin-4-yl (**f**), 3-hydroxypyridin-2-yl (**g**), pyrimidin-2-yl (**h**), 1*H*-benzimidazol-2-yl (**i**), 1,3-thiazol-2-yl (**j**).

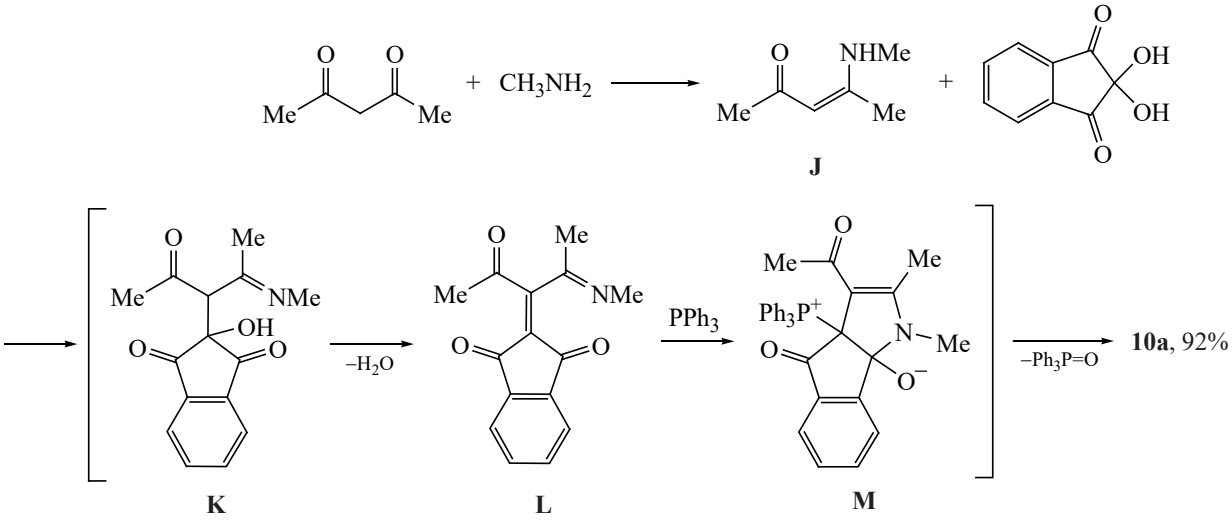
Scheme 5.



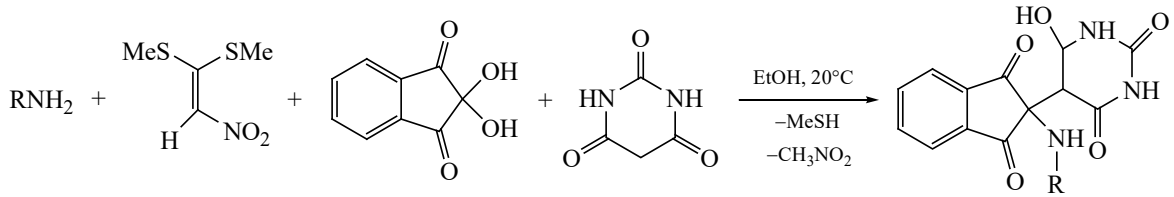
10a–10g, 78–92%

$R^1 = R^2 = Me$ (**a**); $R^1 = Me$, $R^2 = Et$ (**b**); $R^1 = Me$, $R^2 = Ph$ (**c**); $R^1 = Me$, $R^2 = Bn$ (**d**); $R^1 = Me$, $R^2 = 4\text{-}MeOC_6H_4CH_2$ (**e**); $R^1 = OEt$, $R^2 = n\text{-}Pr$ (**f**); $R^1 = OEt$, $R^2 = 4\text{-}MeOC_6H_4$ (**g**).

Scheme 6.



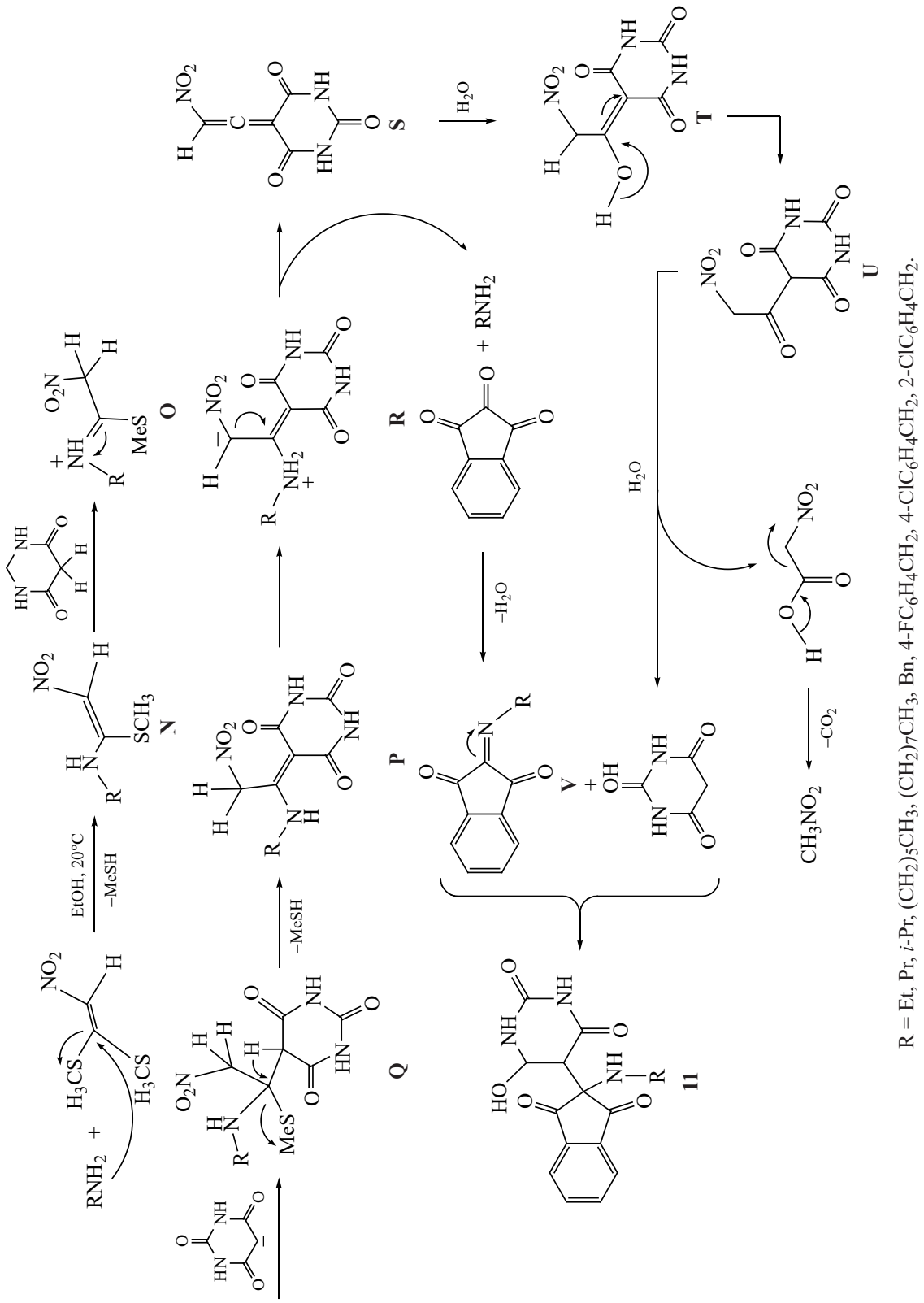
Scheme 7.



11, 67–92%

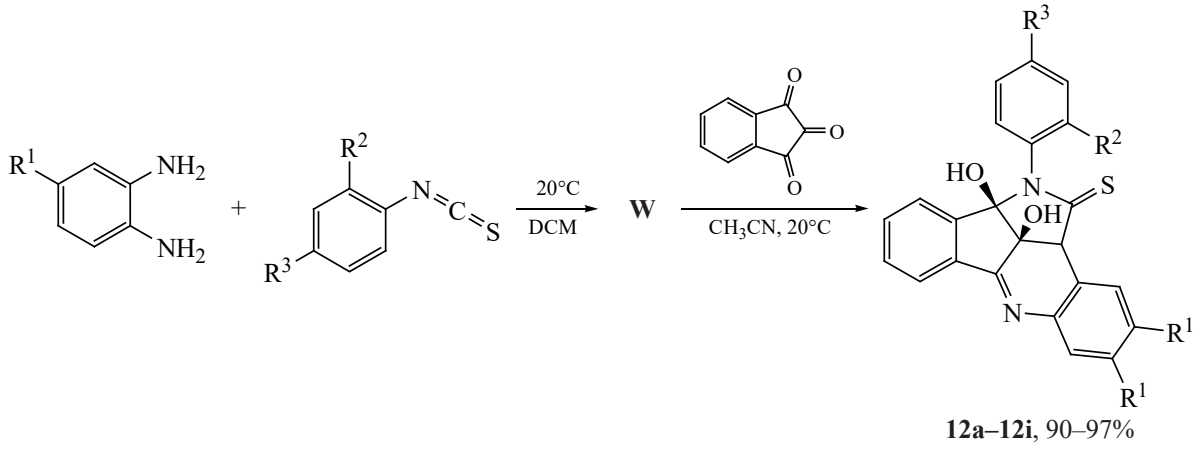
R = Et, Pr, *i*-Pr, $(CH_2)_5Me$, $(CH_2)_7Me$, Bn, $4\text{-}FC_6H_4CH_2$, $4\text{-}ClC_6H_4CH_2$, $2\text{-}ClC_6H_4CH_2$.

Scheme 8.



R = Et, Pr, *i*-Pr, $(CH_2)_5CH_3$, $(CH_2)_7CH_3$, Bn, $4\text{-}FC_6H_4CH_2$, $4\text{-}ClC_6H_4CH_2$, $2\text{-}ClC_6H_4CH_2$.

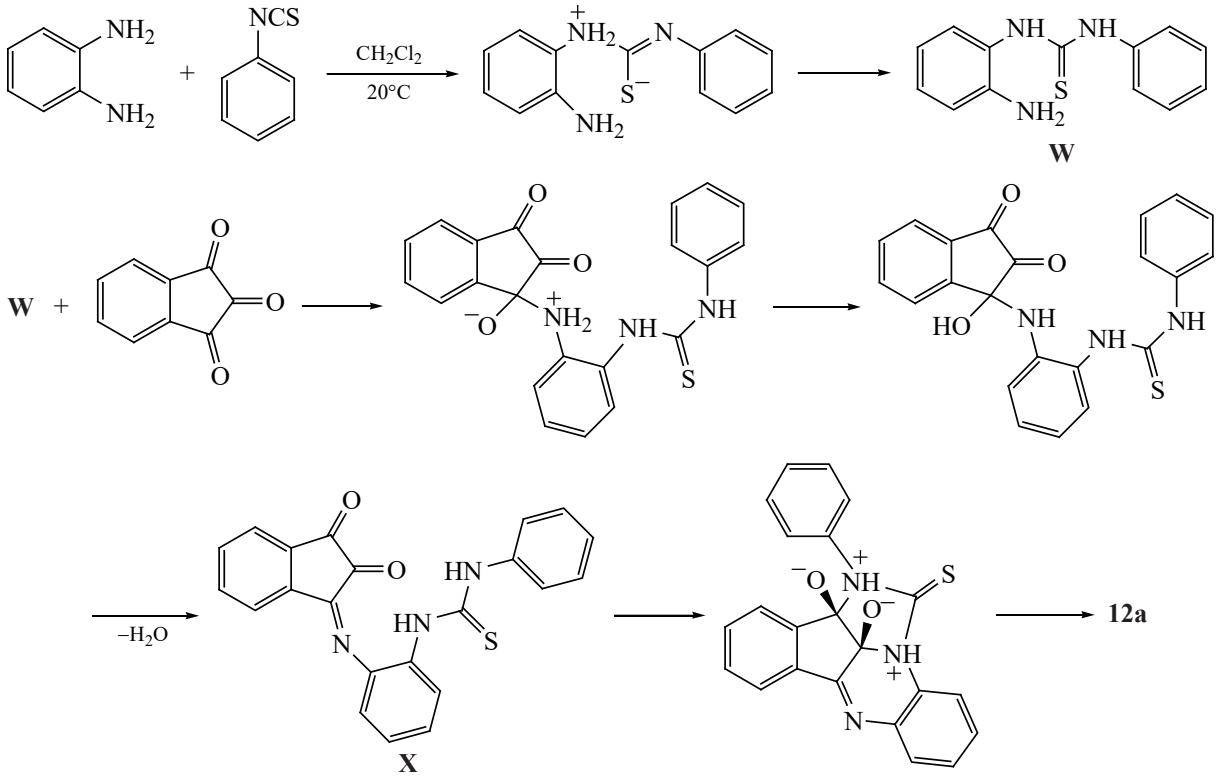
Scheme 9.



12a–12i, 90–97%

$R^1 = R^2 = R^3 = H$ (**a**); $R^1 = Cl$, $R^2 = R^3 = H$ (**b**); $R^1 = Me$, $R^2 = R^3 = H$ (**c**); $R^1 = R^2 = H$, $R^3 = Cl$ (**d**); $R^1 = R^3 = Cl$, $R^2 = H$ (**e**); $R^1 = Me$, $R^2 = H$, $R^3 = Cl$ (**f**); $R^1 = H$, $R^2 = R^3 = Cl$ (**g**); $R^1 = R^2 = R^3 = Cl$ (**h**); $R^1 = Me$, $R^2 = R^3 = Cl$ (**i**).

Scheme 10.



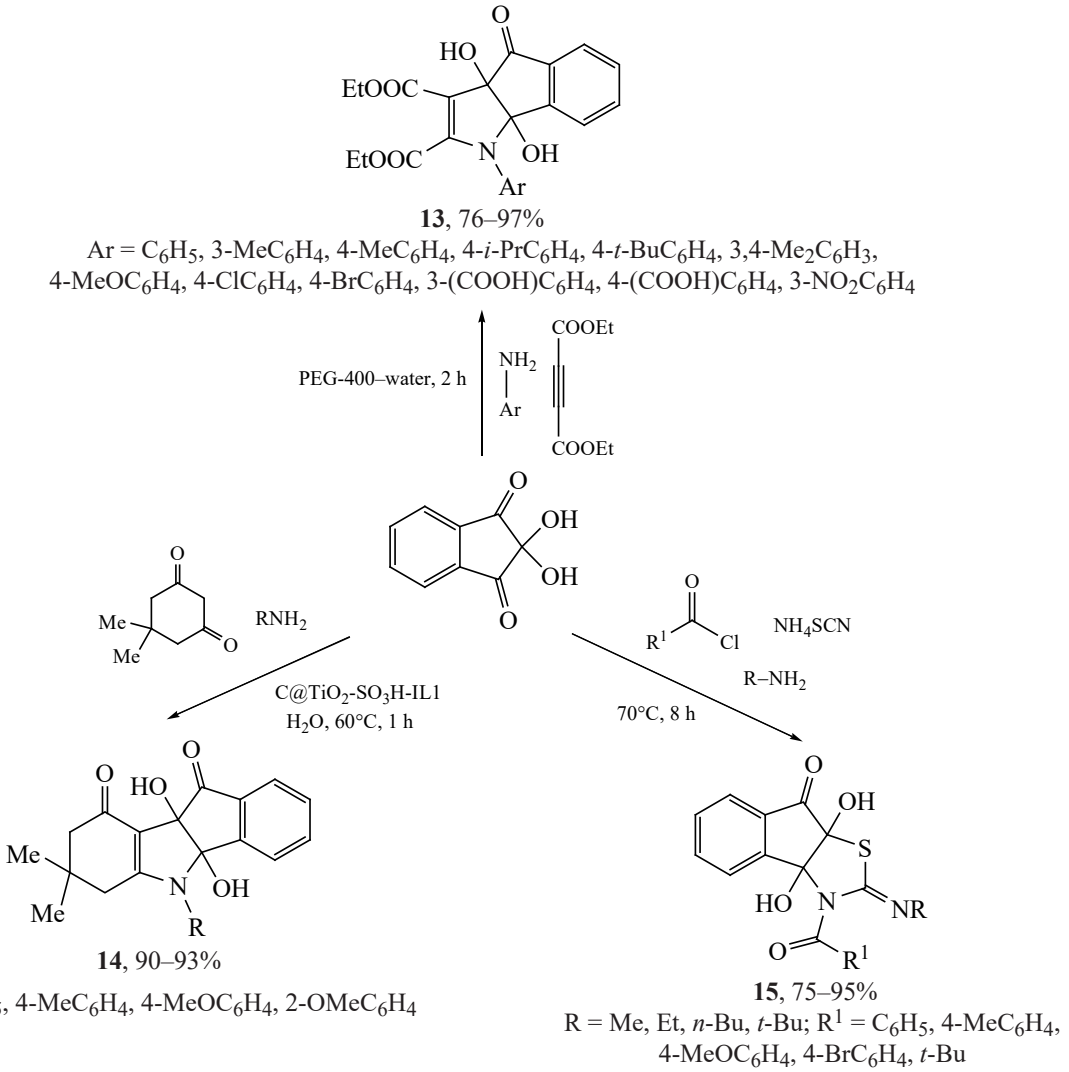
Karami et al. [12] described a convenient synthesis of indeno[1,2-*b*]pyrrol-4(1*H*)-ones **10a**–**10g** by the three-component reaction of ninhydrin, 1,3-dicarbonyl compounds, and primary amines in the presence of triphenylphosphine in acetonitrile at room temperature (Scheme 5). A probable mechanism for the formation of compound **10a** as an example was proposed. Enaminone **J** obtained from pentane-2,4-dione and methylamine reacted as a nucleophile with ninhydrin to produce intermediate **K**. Elimination of a water molecule from **K** gave intermediate **L**, which reacted with PPh_3 to form zwitterion **M**, and the subsequent elimination of triphenylphosphine oxide from **M** furnished product **14a** (Scheme 6).

5-[2-(Alkylamino)-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl]-6-hydroxypirimidine-2,4-(1*H*,3*H*)-diones **11** were synthesized by the one-pot reaction of primary amine, 1,1-bis(methylsulfanyl)-2-nitroethene, ninhydrin, and barbituric acid as an enolizable active methylene compound [13] (Scheme 7). Compounds **11** are likely to be formed according to the mechanism shown in Scheme 8. Intermediate **N** is capable of deprotonating barbituric acid to form stable enolate and intermediate **O** which react with each other to produce intermediate **P**. Next follows elimination of methanethiol from **P**, and intermediate **Q** thus formed is converted to **R** via proton transfer mediated by the amine. The subsequent elimination of amine leads to intermediate **S** which reacts with water to yield nitroenol **T** tautomeric to α-nitro ketone **U**. The hydrolysis of **U** gives barbituric acid and nitromethane. The condensation of the liberated primary amine at the more reactive carbonyl group of ninhydrin at the 2-position yields Schiff base **V**, and the addition of barbituric acid to intermediate **V** results in the formation of target product **11**.

A new convenient synthesis of pentacyclic nitrogen-containing heterocycles **12** was reported in [14]. It is based on successive reactions of *o*-phenylenediamine with aryl isothiocyanate and ninhydrin. The synthetic strategy involving intermediate formation of *N*,*N*′-disubstituted thioamide **W** is simple and environmentally benign, and the target products can be obtained in good yields from cheap commercially available reagents (Scheme 9). A probable mechanism of the formation of compound **12a** is outlined in Scheme 10.

Intermediate **W** obtained from *o*-phenylenediamine and phenyl isothiocyanate readily reacts with ninhydrin

Scheme 11.



13, 76–97%

Ar = C_6H_5, 3-MeC_6H_4, 4-MeC_6H_4, 4-*i*-PrC_6H_4, 4-*t*-BuC_6H_4, 3,4-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-(COOH)C_6H_4, 4-(COOH)C_6H_4, 3-$NO_2C_6H_4$

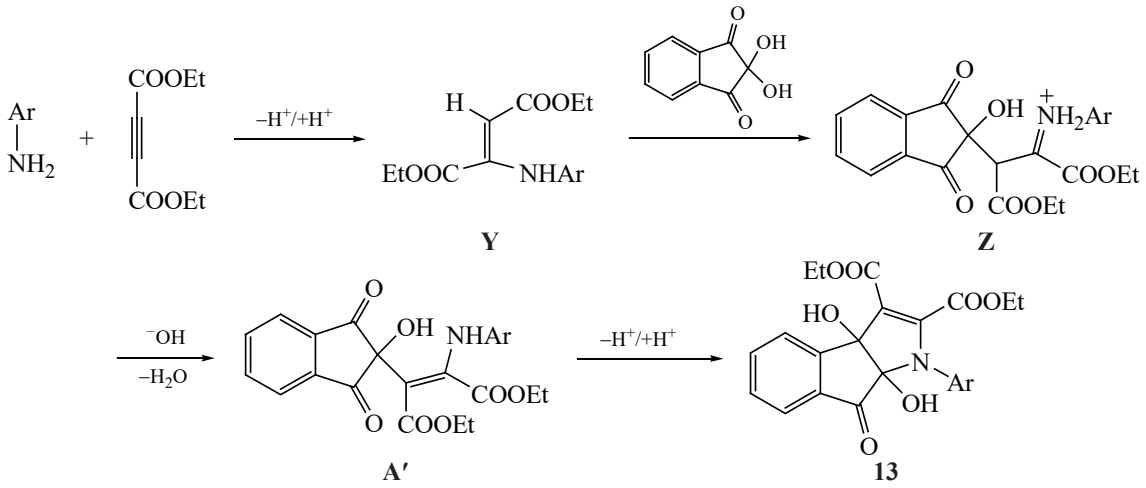
14, 90–93%

R = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$OMeC_6H_4$

15, 75–95%

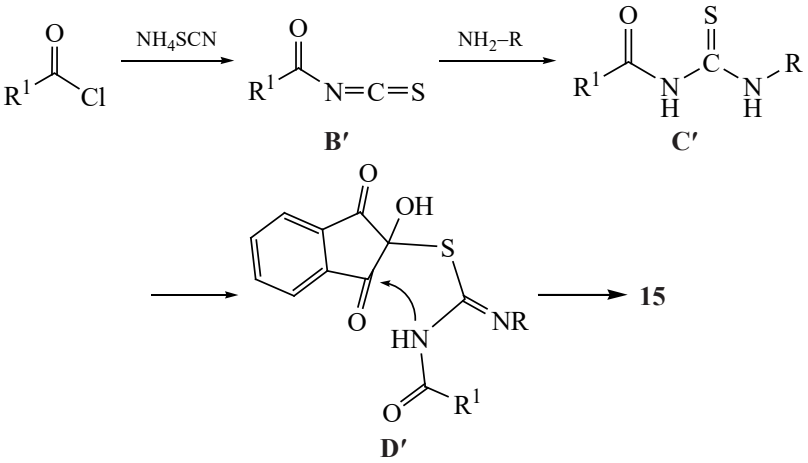
R = Me, Et, *n*-Bu, *t*-Bu; R^1 = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, *t*-Bu

Scheme 12.

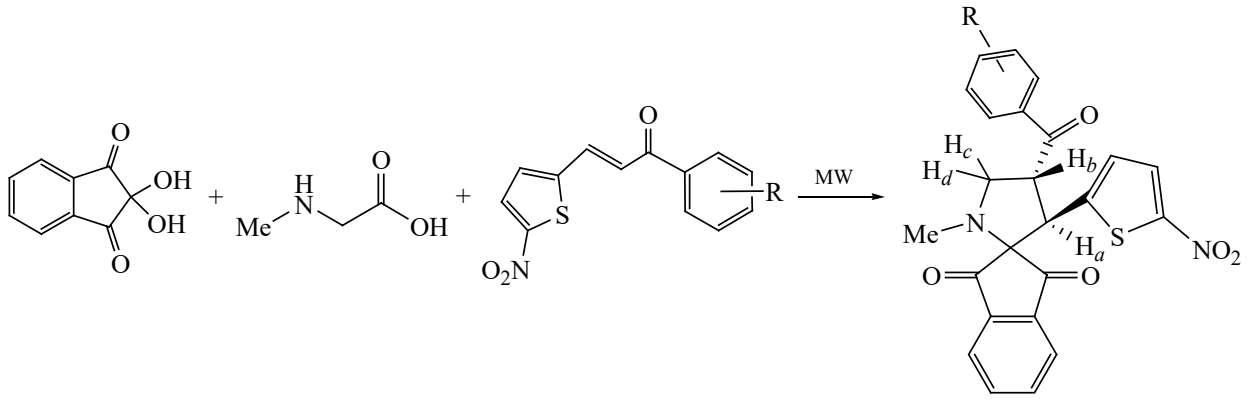


Ar = C_6H_5, 3-MeC_6H_4, 4-MeC_6H_4, 4-*i*-PrC_6H_4, 4-*t*-BuC_6H_4, 3,4-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-(COOH)C_6H_4, 4-(COOH)C_6H_4, 3-$NO_2C_6H_4$.

Scheme 13.



Scheme 14.



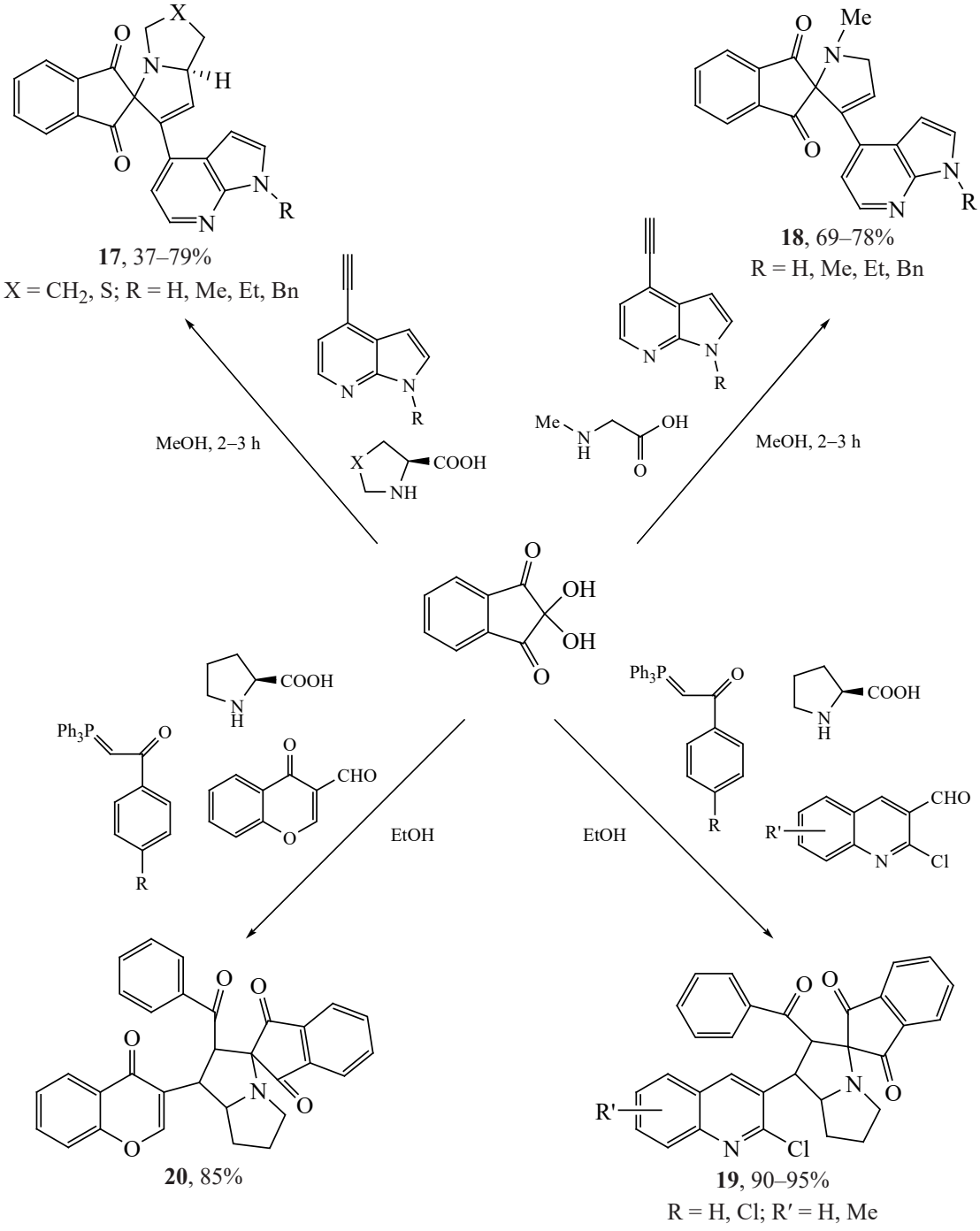
16a–16k, 78–92%

R = 4-Me (**a**), H (**b**), 4-OH (**c**), 4-Cl (**d**), 3-OH (**e**), 4-Br (**f**), 4-MeO (**g**), 4-F (**h**), 4-NO_2 (**i**), 3-Br (**j**), 2-Cl (**k**).

to form intermediate **X** possessing two nucleophilic and two electrophilic centers, which undergoes heterocyclization to product **12a** [15]. When R^1 = H, Cl, Me, R^2 = H, R^3 = Cl or R^1 = H, Cl, R^2 = Cl, R^3 = Cl, only one thioamide was formed, which is not very reactive, and its reaction with ninhydrin led to the regioselective formation of only one product. When R^1 = Me, R^2 = R^3 = Cl, the nucleophilic and electrophilic centers are active, so that two isomeric thioamides and two products were formed.

Dihydroindenopyrroles **13** were synthesized by the reaction of ninhydrin, substituted anilines, and diethyl acetylenedicarboxylate in a mixture of PEG-400 and water [16] (Scheme 11). A probable mechanism

Scheme 15.

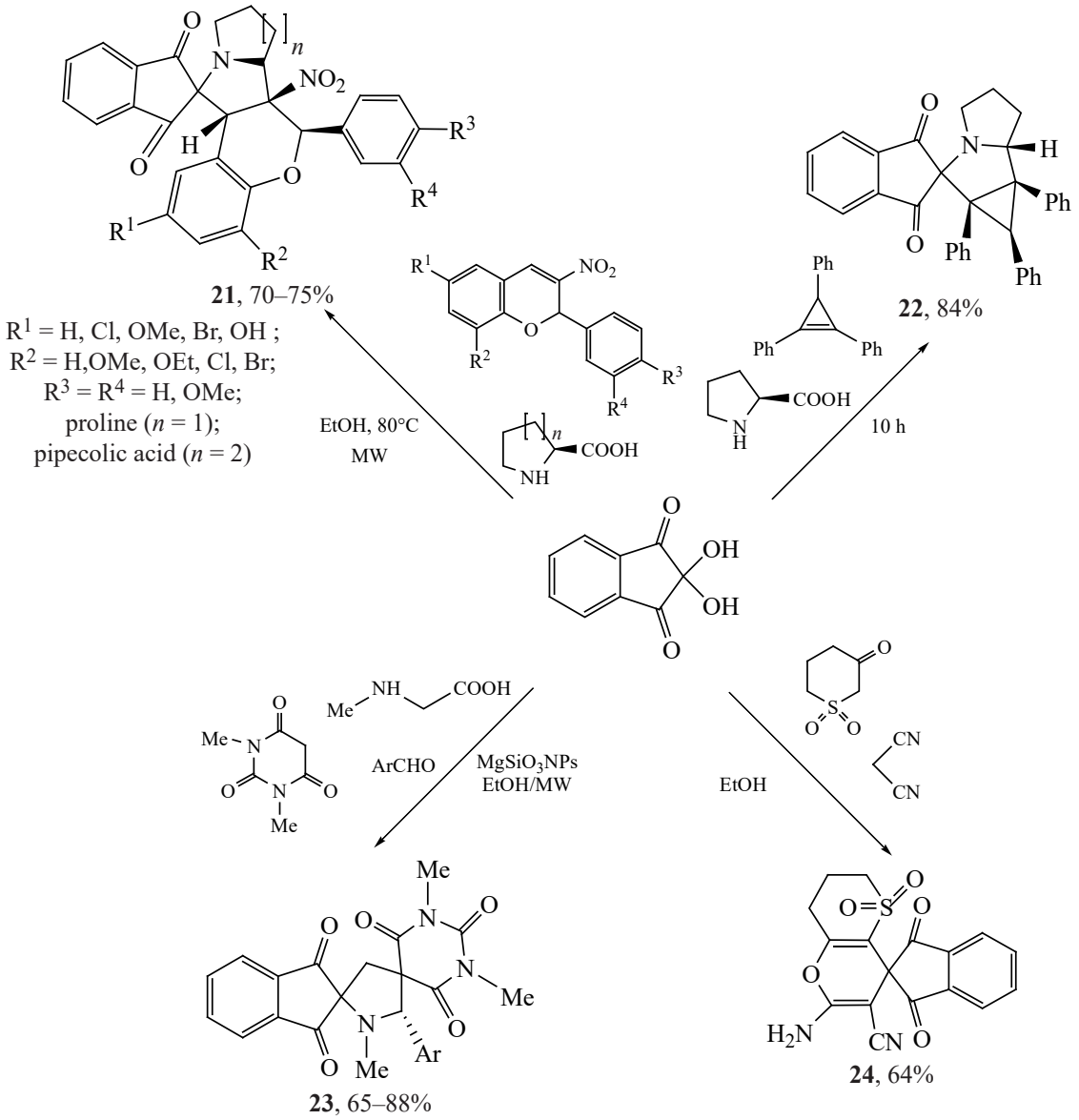


involves the reaction of aromatic amine with the acetylenic diester to form intermediate enamino ester **Y**. Nucleophilic attack of **Y** on the C^2=O carbonyl of ninhydrin gives intermediate **Z**, which undergoes dehydration to produce intermediate **A′**, and intramolecular cyclization of the latter affords target product **13** (Scheme 12).

Indeno[1,2-*b*]indolones **14** were obtained from ninhydrin, anilines, and dimedone in water in the presence of C@TiO_2-SO_3H-IL1 ionic liquid-based solid acid catalyst (Scheme 11) [17]. This new catalyst showed a high activity and stability in water, and the products were obtained in excellent yields. The procedure is environmentally safe, and the catalyst can be readily regenerated and reused up to 5 catalytic runs without significant loss of activity.

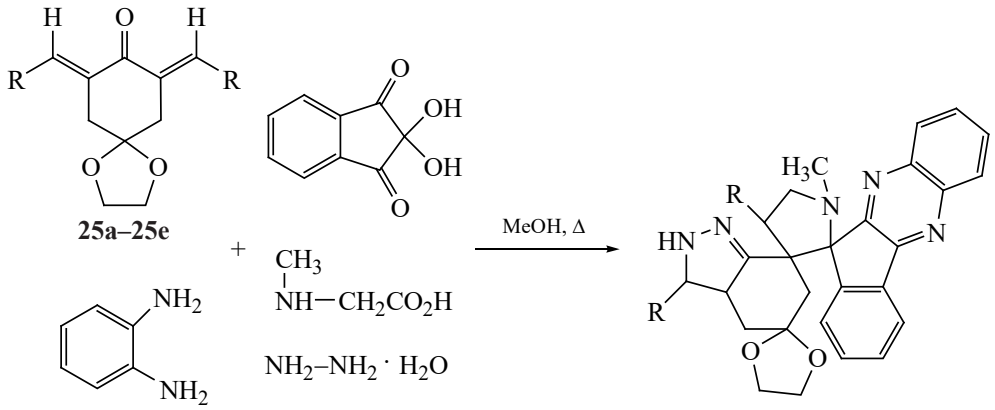
A simple one-pot four-component reaction of ninhydrin, primary amine, acid chloride, and ammonium thiocyanate was used to obtain indenothiazole derivatives **15** under solvent-free conditions [18] (Scheme 11). Scheme 13 shows the proposed mechanism of this transformation. Initially, the reaction of ammonium thiocyanate with acid chloride is likely to produce acyl isothiocyanate **B′** which undergoes

Scheme 16.



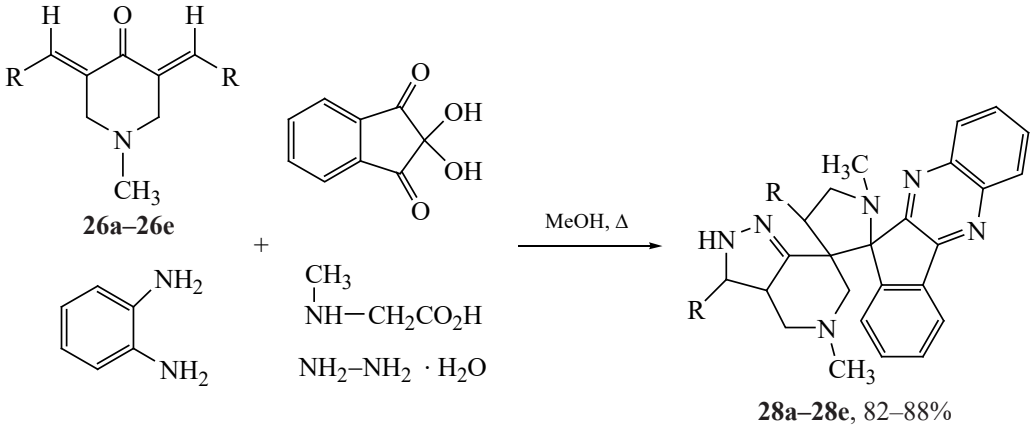
Ar = C_6H_5, 2-NOC_6H_4, 4-NOC_6H_4, 2-MeC_6H_4, 4-BrC_6H_4, 2,3-$F_2C_6H_3$, 3-Cl,4-$OMeC_6H_3$, 1-Cl,4-$OPhC_6H_3$, 2-Me,4-ClC_6H_3, 4-CNC_6H_4, pyridin-4-yl, biphenyl-4-yl.

Scheme 17.



R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-FC_6H_4 (**e**).

Scheme 18.



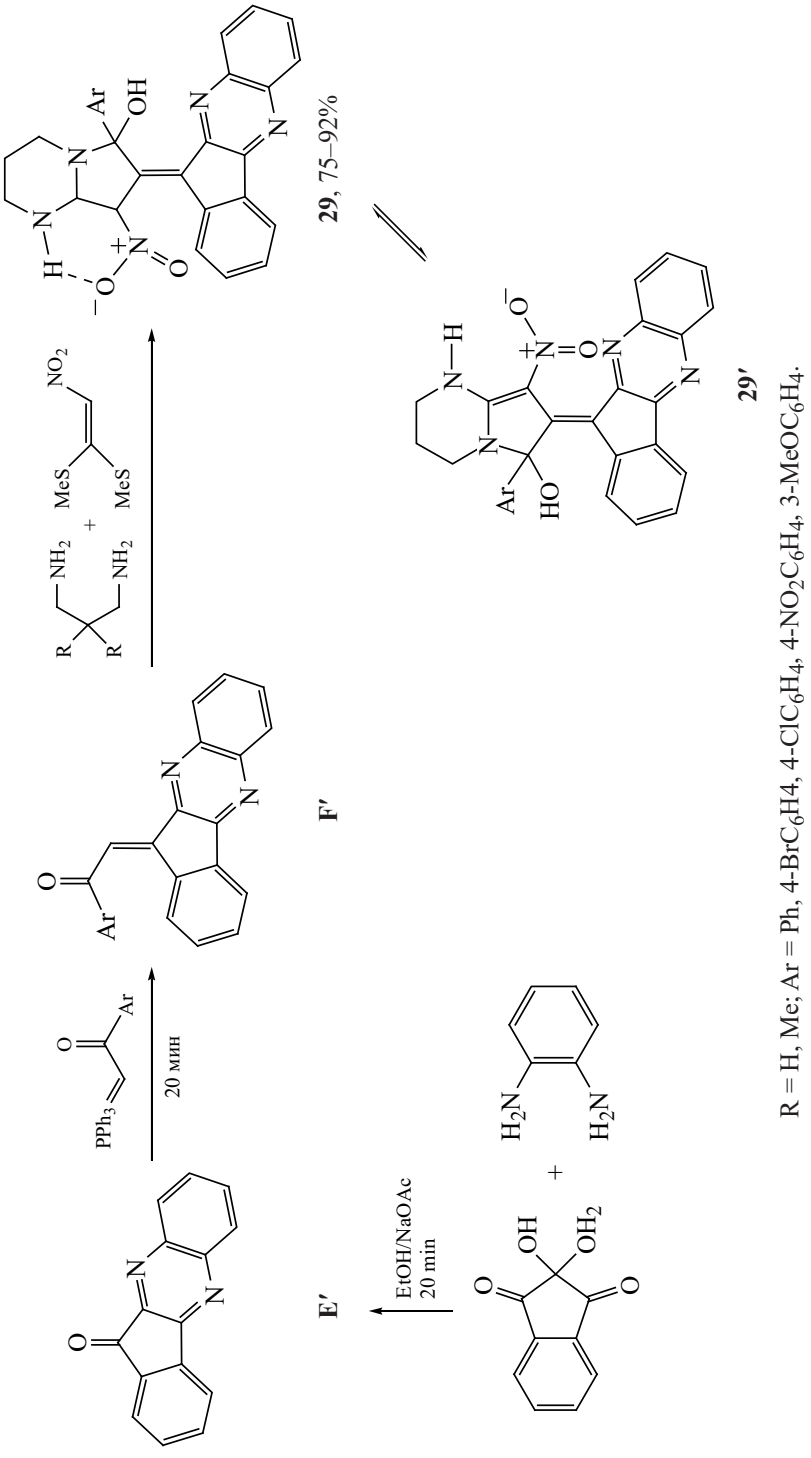
R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), ferrocen-2-yl (**e**).

nucleophilic attack by the amine to give thiourea **C′**. The later attacks the C^2 atom of ninhydrin, and heterocyclization of the resulting intermediate **D′** yields indenothiazole **15**.

Spiro[indene-2,2′-pyrrolidines] **16a**–**16k** were synthesized by the reaction of chalcones containing a nitrothiophene fragment with ninhydrin and sarcosine in the absence of a solvent under microwave irradiation [19] (Scheme 14). A spiro-pyrrolidine skeleton with an azaindole fragment (compounds **17** and **18**) was successfully built up by reacting ninhydrin with proline or sarcosine and 1-alkyl-4-ethynyl-1*H*-pyrrolo[2,3-*b*]-pyridine used as a dipolarophile [20] (Scheme 15). Alizadeh et al. [21] proposed a simple and "green" one-pot method for the synthesis of quinolinyl-substituted spiro-pyrrolizidine derivatives **19** by the sequential four-component reaction of ninhydrin with L-proline, 2-chloroquinoline-3-carbaldehydes, and triphenyl-λ^5-phosphanylidenemethyl ketones [21] (Scheme 15). When 4-oxochromene-3-carbaldehyde was used instead of 2-chloroquinoline-3-carbaldehyde, the corresponding chromenyl-substituted spiro-pyrrolizidine **20** was obtained in 85% yield (Scheme 15). These reactions were characterized by high diastereoselectivity. The proposed reaction mechanism involved Wittig reaction with the aldehydes with the formation of chalcones which reacted as dipolarophiles with azomethine ylides generated from ninhydrin and L-proline.

An interesting approach to the synthesis of nitrochromene-fused spiro-pyrrolidine **21** is based on the three-component reaction of ninhydrin, L-proline (or pipecolic acid), and 2-aryl-3-nitrochromenes as dipolarophiles [22] (Scheme 16). This simple procedure ensured the formation of cycloadducts **21** with excellent regio- and stereoselectivity under both microwave

Scheme 19.


EtOH/NaOAc
20 min
20 мин
E′
F′
29, 75–92%
29′
R = H, Me; Ar = Ph, 4-BrC6H4, 4-ClC6H4, 4-NO2C6H4, 3-MeOC6H4.

irradiation and conventional heating. Indandione **22** spiro-fused to cyclopropapyrrolizine and containing four chiral centers was synthesized by 1,3-dipolar cycloaddition of triphenylcyclopropene and azomethine ylide generated from ninhydrin and L-proline [23] (Scheme 16).

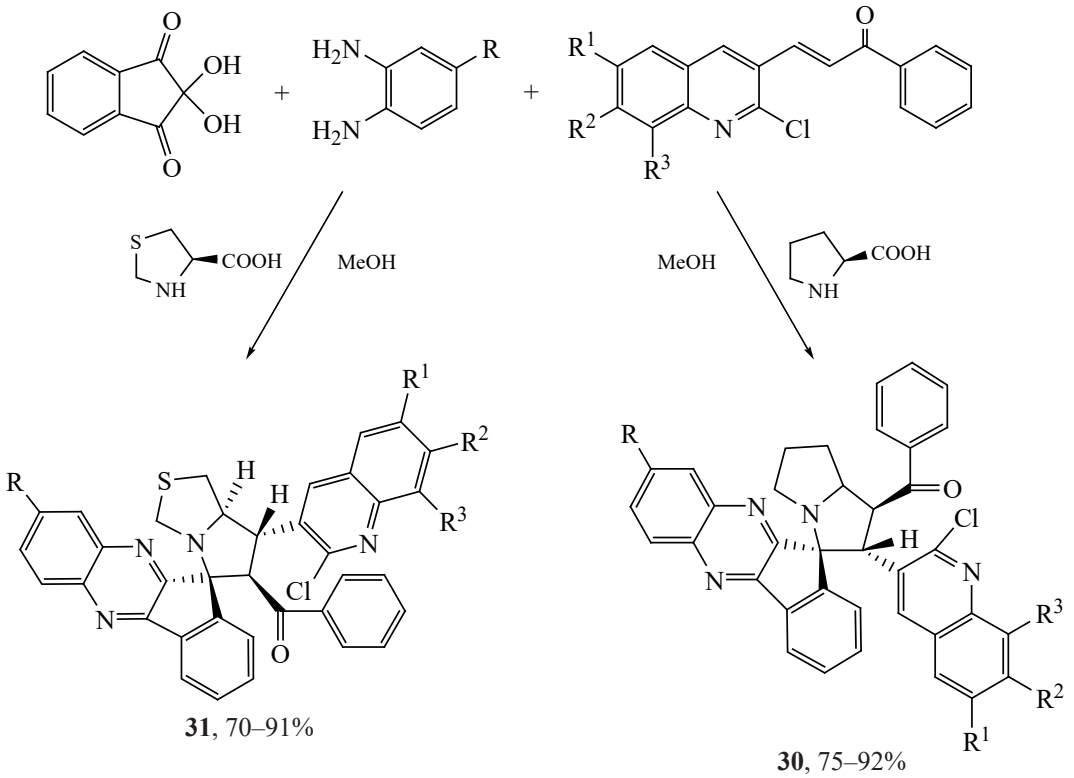
Magnesium silicate nanoparticles ($MgSiO_3$NPs) were found to efficiently catalyze multicomponent reaction of ninhydrin, sarcosine, *N*,*N*-dimethylbarbituric acid, aromatic aldehydes with the formation of dispiropyrrolidine derivatives **23** [24] (Scheme 16). The reactions were complete in 1–1.5 h under microwave irradiation. Compounds **23** showed antibacterial activity and antiproliferative activity against some cell lines. New spiro-thiopyranopyran derivative **24** was synthesized by the reaction of dihydro-2*H*-1λ^6-thiopyran-1,1,3(4*H*)-trione, ninhydrin, and malononitrile [25] (Scheme 16). The high rate of formation of compound **24** was determined by the high reactivity of the cyclic keto sulfone.

New hybrid spiro-indenoquinoxaline-pyrrolidines **27** and **28** were obtained as a result of five-component reactions of ninhydrin, *o*-phenylenediamine, sarcosine, hydrazine hydrate, and 1,4-dioxaspiro[4.5]decanes **25** (Scheme 17) or (3*E*,5*E*)-3,5-bis(arylmethylidene)-1-methylpiperidin-4-ones **26** (Scheme 18) as dipolarophiles [26, 27]. In both cases, the proposed mechanism involved intermediate formation of azomethine ylide, 1,3-dipolar cycloaddition to one of the exocyclic double bonds of dipolarophile **25** or **26**, and cyclization with hydrazine hydrate. Intermediate azomethine ylide was generated from indenoquinoxalin-11-one resulting from the reaction of ninhydrin with *o*-phenylenediamine and sarcosine.

Alizadeh et al. [28] reported a "green" regioselective synthetic approach to new indenoquinoxaline derivatives **29** containing a pyrrolopyrimidine moiety (Scheme 19). According to the proposed mechanism, indenoquinoxaline **E′** derived from ninhydrin and *o*-phenylenediamine reacts with 1-aryl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one to give (*E*)-phenacylidene intermediate **F′**. The subsequent reaction of **F′** with 1,3-diamine and 1,1-bis(methylsulfanyl)-2-nitroethene under ultrasonication afforded final product **29** in equilibrium with its isomer **29′**.

Spiro-indenoquinoxaline-pyrrolizines **30** were synthesized from ninhydrin, substituted *o*-phenylenediamines, proline, and quinoline-based chalcones as dipolarophiles [29]. The same authors later reported [30] the synthesis of pyrrolothiazole derivatives **31**

Scheme 20.

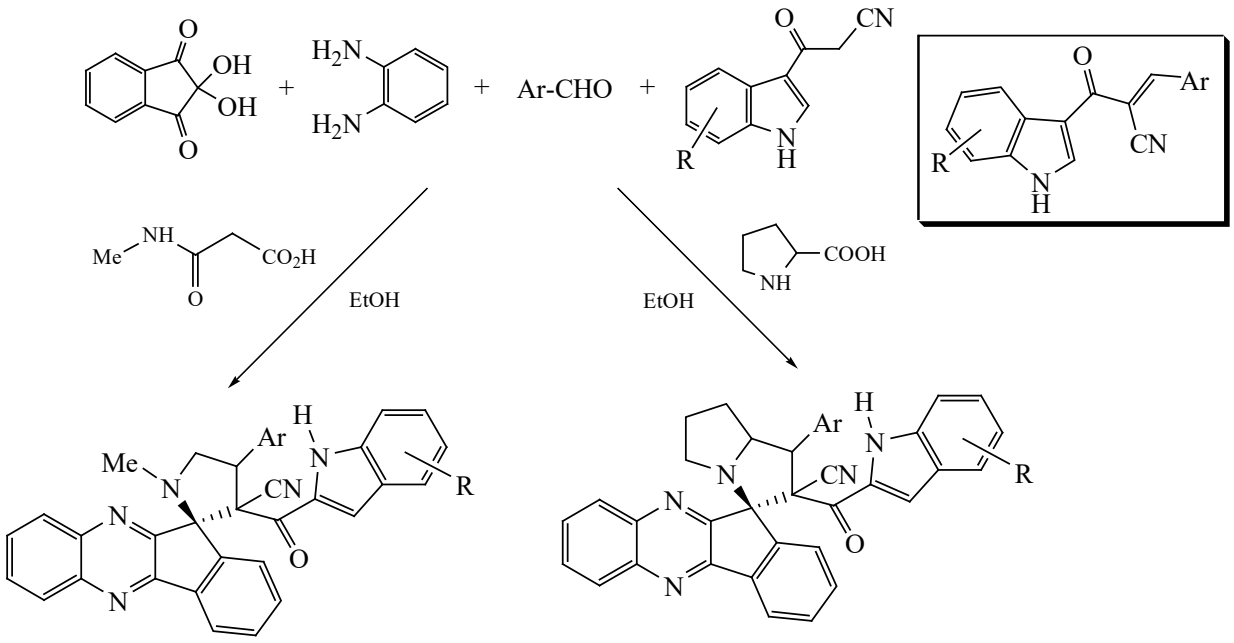


31, 70–91%

30, 75–92%

R = H, COC_6H_5; R^1, R^2, R^3 = H, CH_3, OCH_3.

Scheme 21.



32, 55–79%

Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-MeC_6H_4, 2-ClC_6H_4, 3-$NO_2C_6H_4$, 3-ClC_6H_4, 2,3-$(OMe)_2C_6H_3$, 2,4-ClC_6H_3, thiophen-2-yl, naphthalen-1-yl

33, 69–93%

Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-ClC_6H_4, 2,3-$(OMe)_2C_6H_3$, thiophen-2-yl; R = H, 1-Me, 7-Me

using thiazolidine-2-carboxylic acid instead of proline (Scheme 20). The synthesized compounds were tested for in vitro antioxidant activity and in vivo cytotoxic activity against breast cancer (MCF-7) and lung adenocarcinoma (A-549) cell lines [30].

New spiro-indenoquinoxaline-pyrrolidines **32** and -pyrrolizidines **33** containing an indole fragment were synthesized by the five-component reaction of ninhydrin, *o*-phenylenediamine, amino acids, 3-(2-cyanoacetyl)indoles, and aromatic aldehydes in ethanol [31] (Scheme 21). Here, the Knoevenagel condensation product of cyanoacetylindole and aromatic aldehyde acted as a dipolarophile. It should be noted that no target products were obtained when primary amino acids such as glycine or phenylalanine were used.

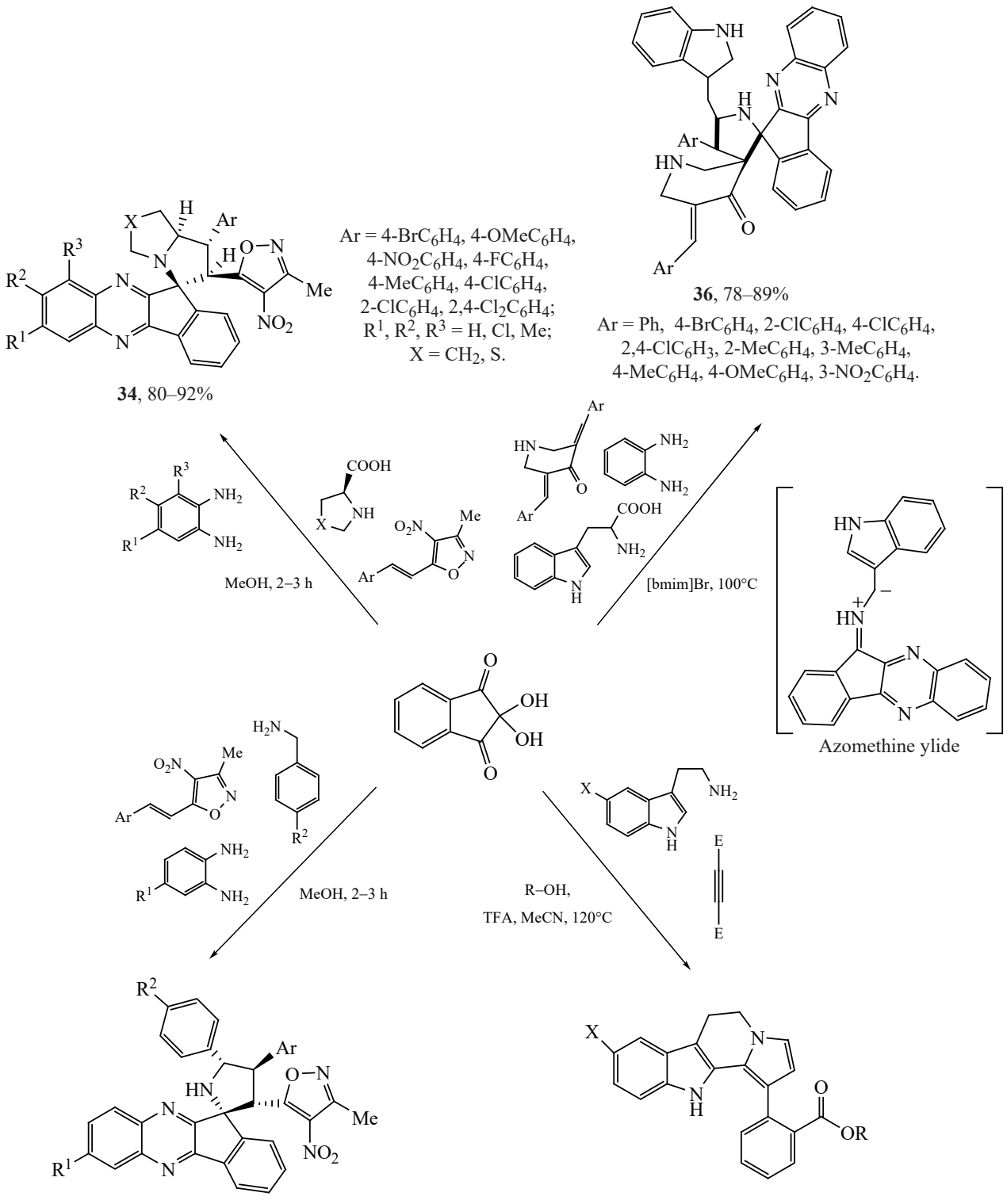
Gupta and Khurana [32] developed a convenient synthesis of isoxazolyl-substituted spiro-indenoquinoxaline-pyrrolizines **34** via four-component reaction of ninhydrin, substituted *o*-phenylenediamines, L-proline (or thioproline), and 3-methyl-4-nitro-5-styrylisoxazoles in methanol (Scheme 22). The described procedure is simple and catalyst-free, and the products were formed with high regioselectivity in short reaction times.

Compounds **35** were synthesized with high regio- and diastereoselectivity by the four-component condensation of benzylamines, ninhydrin, *o*-phenylenediamines, and substituted isoxazoles, which involved [3+2]-cycloaddition [33] (Scheme 22). It was shown that the nature and position of substituents in the aromatic rings of styrylisoxazole (dipolarophile), benzylamine, and *o*-phenylenediamine affected the diastereoselectivity.

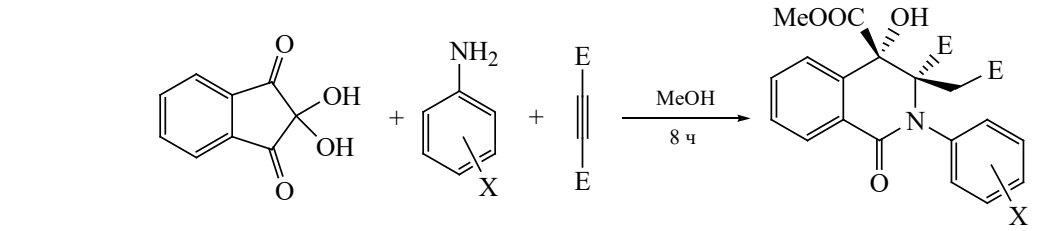
Arumugan et al. [34] described the synthesis of new dispiropirrolidine hybrids **36** with the use of [bmim]Br ionic liquid. A probable mechanism of this reaction involves in situ generation of azomethine ylide from indenoquinoxalinone and L-tryptophane and regioselective 1,3-dipolar cycloaddition to bis(arylmethylidene)piperidinone (Scheme 22). Biological screening of compounds **36** revealed their inhibitory activity against acetyl- and butyrylcholinesterases. Recent advances in the synthesis of spiro compounds based on indeno[1,2-*b*]quinoxalines were reviewed in [35].

Dihydroindolizino[8,7-*b*]indoles **37** were obtained via a four-component approach based on the reaction of ninhydrin, substituted tryptamine, dialkyl acetylenedicarboxylate, and various aliphatic alcohols in aceto-

Scheme 22.

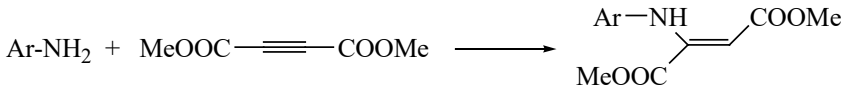

Ar = 4-BrC6H4, 4-OMeC6H4, 4-NO2C6H4, 4-FC6H4, 4-MeC6H4, 4-ClC6H4, 2-ClC6H4, 2,4-Cl2C6H4; R1, R2, R3 = H, Cl, Me; X = CH2, S.
34, 80–92%
36, 78–89%
Ar = Ph, 4-BrC6H4, 2-ClC6H4, 4-ClC6H4, 2,4-ClC6H3, 2-MeC6H4, 3-MeC6H4, 4-MeC6H4, 4-OMeC6H4, 3-NO2C6H4.
MeOH, 2–3 h
[bmim]Br, 100°C
Azomethine ylide
MeOH, 2–3 h
R–OH, TFA, MeCN, 120°C
35, 70–92%
Ar = Ph, 4-FC6H4, 4-ClC6H4, 2-ClC6H4, 4-BrC6H4, 2-BrC6H4, 4-NO2C6H4, 4-OMeC6H4, 2-OEtC6H4, anthryl, furyl, thienyl; R1 = H, Me, NO2; R2 = H, F, OMe.
37, 65–87%
X = H, OMe; R = Me, Et, Pr; E = COOMe, COOEt.

Scheme 23.

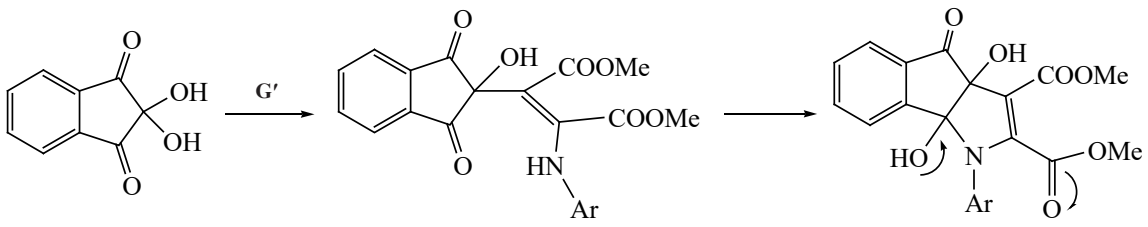


38, 68–82%

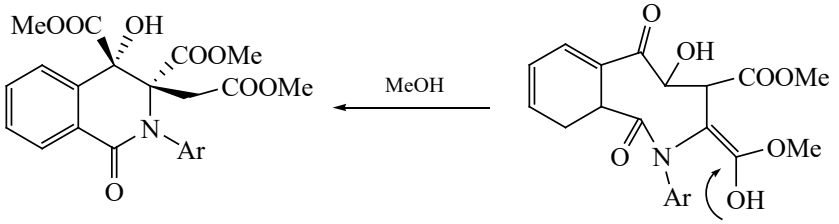
E = COOMe, COOEt; X = H, 4-F, 4-Br, 4-I, 4-Me, 2-F, 3,4-Me_2, 3,5-Me_2, 4-OCF_3.



G′



H′ **I′**



37 **J′**

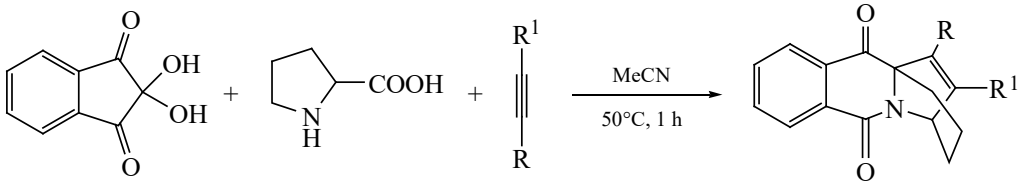
Ar = Ph, 4-FC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-MeC_6H_4, 2-FC_6H_4, 3,4-$(Me)_2C_6H_3$, 3,5-$(Me)_2C_6H_3$, 4-$OCF_3C_6H_4$.

nitrile [36] (Scheme 22). The transformation sequence is likely to include Pictet–Spengler and Michael reactions and nucleophilic addition, leading to the formation of new C–C and C–N bonds. It is notable that the heterocycle is formed as a result of double tandem cyclization catalyzed by trifluoroacetic acid.

Shirsat et al. [37] studied the three-component reaction of ninhydrin, anilines, and acetylenedicarboxylic acid esters in methanol with the diastereoselective formation of *N*-aryl-dihydroisoquinolin-2(1*H*)-ones **38** (Scheme 23). In the first stage, the addition of aniline to the triple bond of acetylenedicarboxylate gives intermediate **G′** which reacts with ninhydrin to produce adduct **H′**. The latter undergoes intramolecular cyclization to structure **I′**, and pinacol–pinacolone type rearrangement of **I′** leads to intermediate **J′**. Methanolysis of **J′** is accompanied by intramolecular cyclization to afford the desired product **38** with excellent diastereoselectivity. The reaction can be regarded as nitrogen insertion with the formation of isoquinolinone skeleton. The stereostructure of **38** was determined by X-ray analysis (CCDC entry no. 1588852) [37].

A convenient tandem one-pot approach to access pyrido[1,2-*b*]isoquinoline derivatives **39** was developed with the use of readily available ninhydrin, proline, and alkynes [38] (Scheme 24). The reaction involves [3+2]-cycloaddition of alkynes and 1,3-dipole generated in situ from ninhydrin and proline. It is important that two new C–N bonds, three C–C bonds, and three new rings were formed in one step.

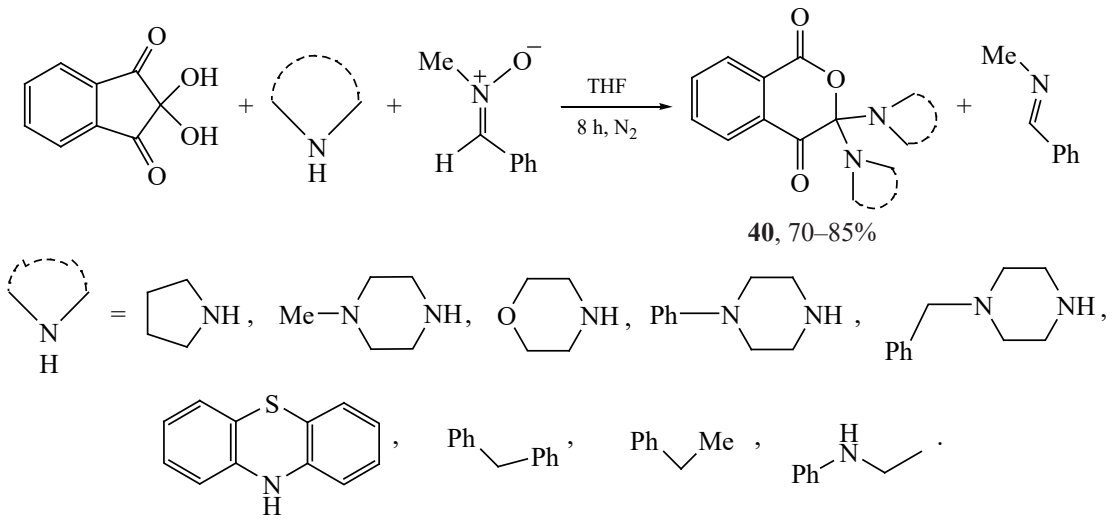
Scheme 24.



39, 67–90%

R = Ph, 3-OMeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CFC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-MeC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-EtC$_6$H$_4$, 3-NH$_2$C$_6$H$_4$, thiophen-2-yl, thiophen-3-yl, SiMe$_3$; R^1 = H, COOMe, COOEt.

Scheme 25.



40, 70–85%

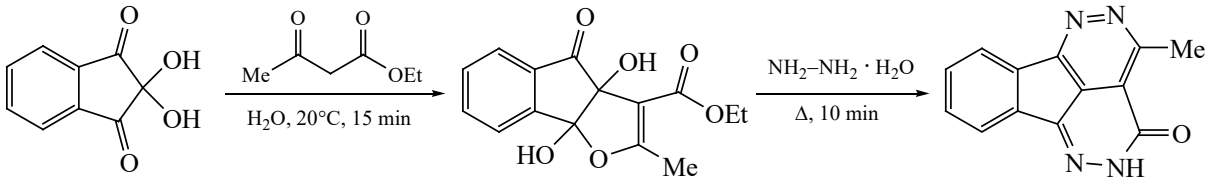
3,3-Disubstituted isochroman-1,4-diones **40** were synthesized by the three-component reaction of ninhydrin, secondary amines, and *N*-methyl-*C*-phenylnitrone [39] (Scheme 25). In fact, the nitrone acted as an oxygen donor, and the corresponding Schiff base was formed as a by-product. Interestingly, most of the obtained isochroman-1,4-dione derivatives **40** in solution showed fluorescence with high quantum yields.

3. SYNTHESIS OF POLYHETEROCYCLES BY REACTIONS OF NINHYDRIN WITH ALIPHATIC, ALICYCLIC, AROMATIC, AND HETEROCYCLIC COMPOUNDS

It is known that ninhydrin reacts with ethyl acetoacetate in water at room temperature to give ethyl indeno[1,2-*b*]furan-3-carboxylate **41** in almost quantitative yield [40]. In continuation of these studies, a green synthesis of 4-methyl-1,2,5,6-tetraazafluoranten-3(2*H*)-one (**42**) by the condensation of **41** with hydrazine hydrate in water was reported [41] (Scheme 26). Compound **42** was treated with Lawesson's reagent to obtain tetraazafluoranthene-3-thione **43**, and the alkylation of **42** and **43** at the nitrogen or sulfur atom afforded the corresponding alkyl derivatives **44** and **45** (Scheme 27).

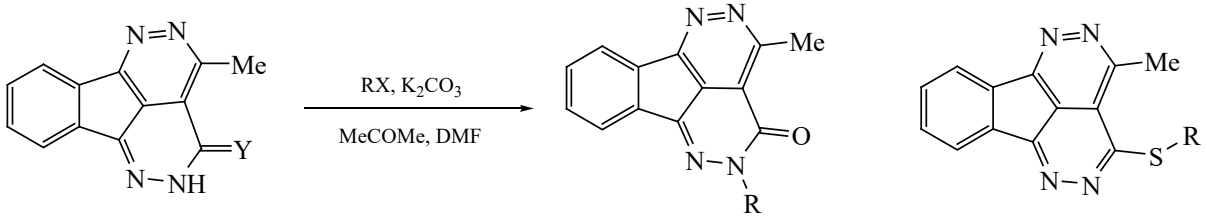
Cyclic hemiketals **46** obtained from phenols and ninhydrin are of considerable interest for the design of various heterocyclic scaffolds, including derivatives of spiro-benzofuran-isobenzofuran (**47**) [42], benzodiazonine (**48a**) [43], 2,5-benzodiazocin-1(2*H*)one (**48b**) [44], phthalimide (**49**) [45, 46], quinoxaline (**50**) [47], pyridazine [48], isoindole (**51**) [49, 50], and propellane (**52**) [51, 52]. The reactions of isoindole **51** with malononitrile in ethanol in the presence of triethylamine and with 2-bromomalononitrile in DMF in the presence of potassium carbonate gave compounds **53** and spiro-benzofurans **54**, respectively [49] (Scheme 28). Antibiotics [53, 54] and drugs for the therapy of neurodegenerative diseases (such as Alzheimer's and Parkinson's diseases) [54] were found among compounds of the propellane series. Propellanes

Scheme 26.



41 **42**, 54%

Scheme 27.



42, **43** **44a–44e**, 65–85% **45a**, **45b**, **45e**, 79–90%

Y = O (**41**), Y = S (**43**); **44**, **45**, R = allyl (**a**), Bn (**b**), $CH_2(CO)Ph$ (**c**), $CH_2(CH_2)_3CH_3$ (**d**), CH_2CO_2Et (**e**).

are likely to be formed via initial addition of triphenylphosphine to dialkyl acetylenedicarboxylate to produce 1,3-dipole **K′** whose protonation yields vinylphosphonium cation **L′**. Nucleophilic attack of conjugate base **M′** on **L′** leads to intermediate **N′** which undergoes intramolecular 6-*endo*-trig-cyclization to form the propellane skeleton of **52**. It is worth noting that only one stereoisomer was obtained in this reaction, but the exact orientation of the ester groups (*cis* or *trans*) in final products **52** was not determined (Scheme 29).

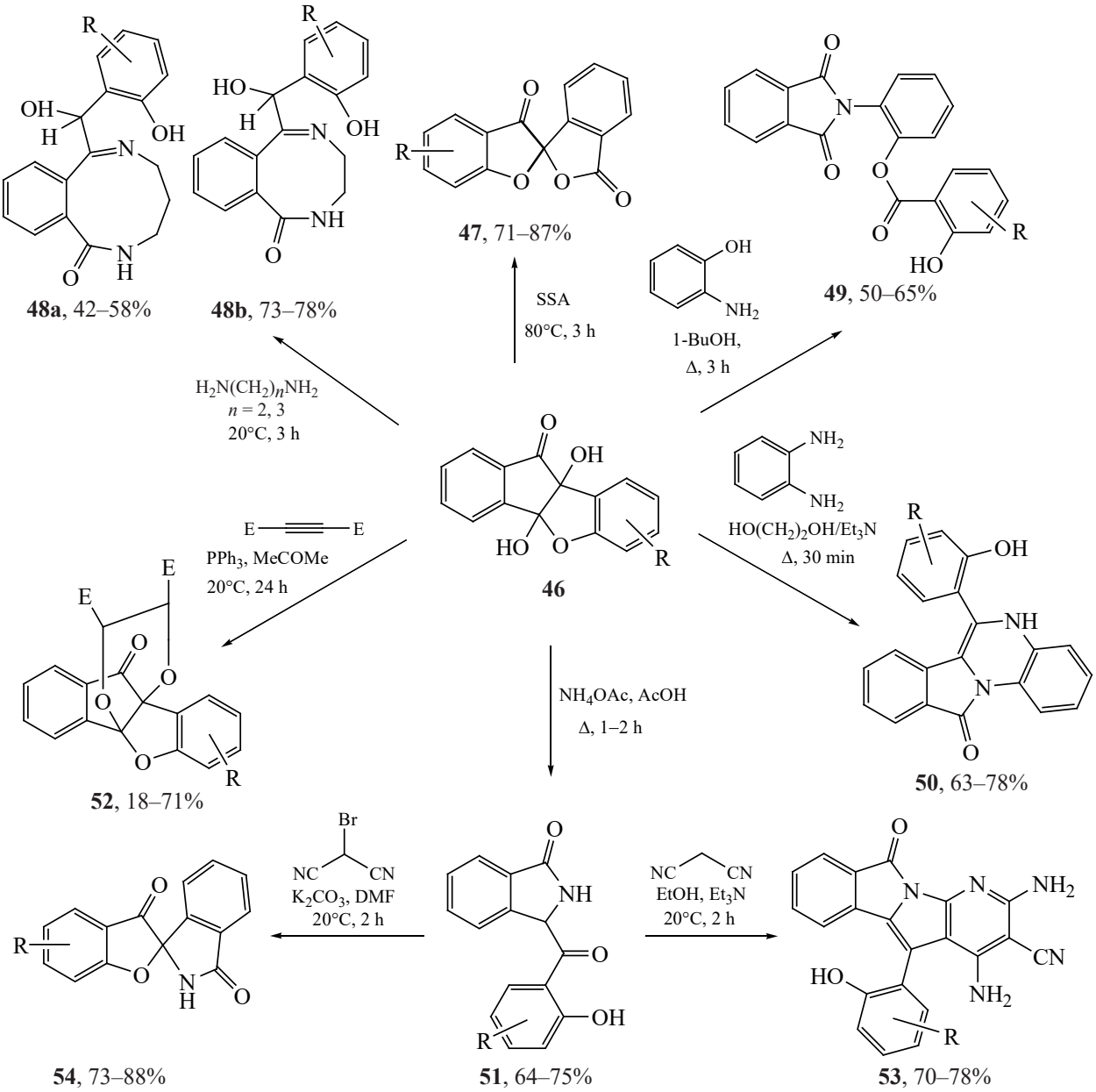
El-Sayed et al. [54] described the cyclocondensation of ninhydrin and pyrimidine-4-thiol **55** in an aqueous solution of sodium carbonate, which led to the formation of thienopyrimidine **56**, presumably through intermediate **O′** (Scheme 30). The reaction involves dehydration, followed by the addition of the sulfanyl group to carbonyl and cyclization. Thieno[2,3-*d*]pyrimidine **56** was obtained in 65% yield.

The synthesis polycyclic organic molecules with fused heterocyclic moieties is of great significance due to structural similarity of such molecules to those of natural origin [1, 2]. Compounds containing a fused indeno[1,2-*b*]indole fragment are known to exhibit various biological activities [55, 56]; therefore, much attention has been given in recent years to the synthesis of indeno[1,2-*b*]indole derivatives. 4b,9b-Dihydroxy-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-diones **57** are mainly accessed through reactions of ninhydrin with amino derivatives of 1,3-dicarbonyl compounds [57], alkyl propiolates [58], dialkyl acetylenedicarboxylates [59], and 1,1-bis(methylsulfanyl)-2-nitroethenes [60]. All these methods are based on the in situ generation of intermediate enaminone (or enamino ester) which then reacts with ninhydrin [55]. Compounds **57** were synthesized in [61, 62] using lactic acid as a catalyst. Compound **57a** was obtained in 41% yield in the presence of a catalytic amount of acetic acid, whereas the use of lactic acid improved the yield to 46%. By optimization experiments, an amount of lactic acid necessary to achieve the maximum yield (87%) of **57a** was determined. Under the optimized conditions, lactic acid catalyzed the synthesis of a number of other derivatives **57b**–**57j** (Scheme 31).

New spiro-isobenzofuran derivatives **58** and **59** were synthesized in good yields by successive condensation/oxidation of ninhydrin with 4-amino-1,2-naphthoquinones or 2-amino-1,4-naphthoquinones [63] (Scheme 32). All reactions were carried out in one pot in two stages. The condensation was performed in acetic acid at 70–100°C, and the oxidation stage, in the presence of H_5IO_6 at room temperature.

Based on the chemical properties of ninhydrin as a cyclic polyketone and 1,3-binucleophile nature of enaminones like 4-(alkyl- or arylamino)naphthalene-1,2-diones, the formation of 6b,11b-dihydroxybenzo[*g*]indeno[1,2-*b*]indole **P′** could be expected as a result

Scheme 28.

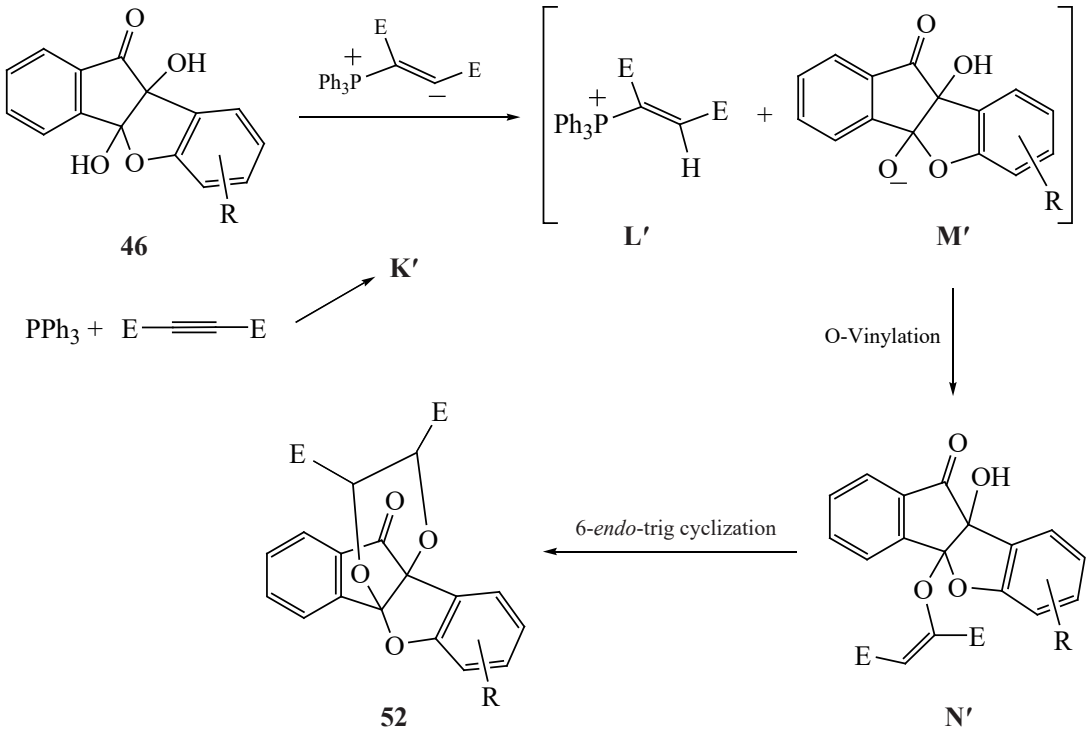


47, R = 2-Me, 4-Me, 4-F, 2-Cl, 4-Cl, 2,4-Cl_2, 4-Cl, 3-Me, 4-Br, 4-OMe, 4-Ph, 4-*i*-Pr, 2,3-benzo-, 4,5-benzo-; **48a**, R = H, 3-Me, 5-Me, 3-OMe, 5-OMe, 3-Cl, 5-Cl, 5-Br; **48b**, R = 3-$NHCO_2Me$, 4-$NHCO_2Me$, 5-$NHCO_2Me$, 3,5-(*t*-Bu)$_2$, 1-Ad, 5-Me; **49**, R = 2-OMe, 4-OMe, 2-Me, H, 2-Cl, 4-Cl, 4-Br; **50**, R = H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-Cl, 4-Cl, 4-Br; **51**, **53**, **54**, R = H, 2-Me, 3-Me, 4-Me, 4-F, 2-Cl, 4-Cl, 4-Br, 4-Cl, 3-Me, 2,4-Cl_2, 2-Ph, 4-OMe, 4-CO_2Me, 2,3-benzo-, 4,5-benzo-; **52**, R = H, 2,3-benzo-, 4-*t*-Bu, 3-OH, E = CO_2Et, CO_2Me.

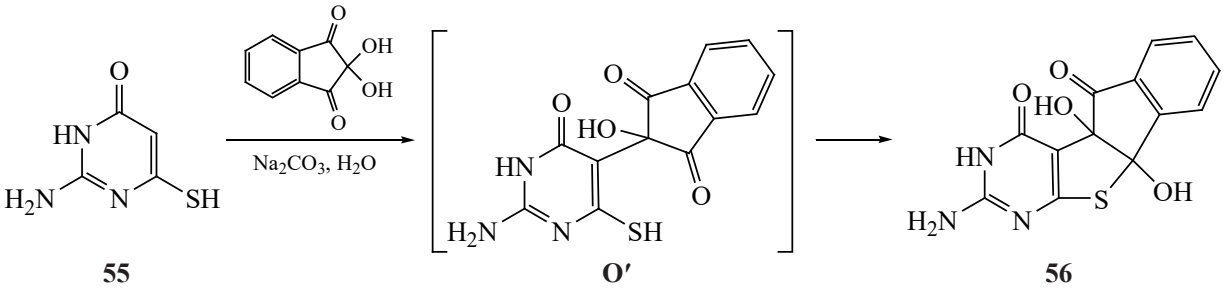
of the condensation of ninhydrin with enaminone. This assumption was confirmed by the isolation of intermediate diols **P′** in the synthesis of **58b** and **59e**. The subsequent oxidative cleavage of **P′** by the action of periodic acid afforded benzo[*f*]naphtho[1,2-*b*]azocine **Q′** (Scheme 33).

Due to relatively strong attraction between the nitrogen atom and C^8=O carbonyl group, the former acquires a larger positive charge, so that benzo[*f*]-naphtho[1,2-*b*]azocine **Q′** is prone to hydrolysis with the formation of 2-(2-benzo[*g*]indolyl)benzoic acid **S′**. Compounds **58** are formed by cyclization of **S′** through

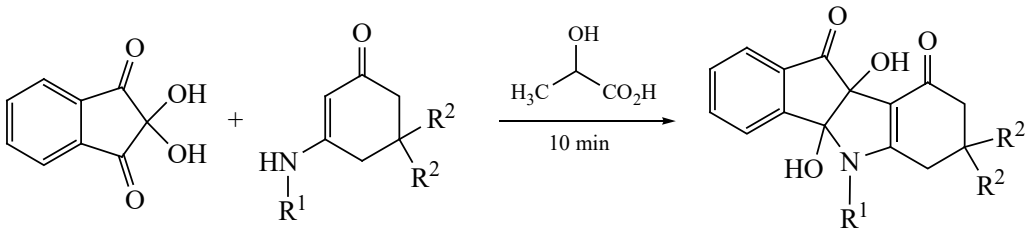
Scheme 29.



Scheme 30.

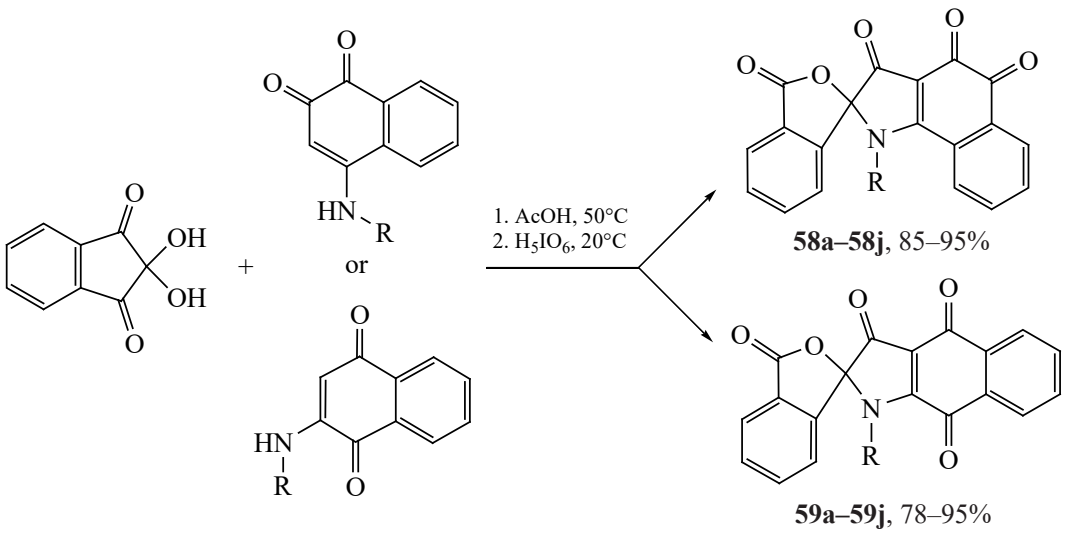


Scheme 31.



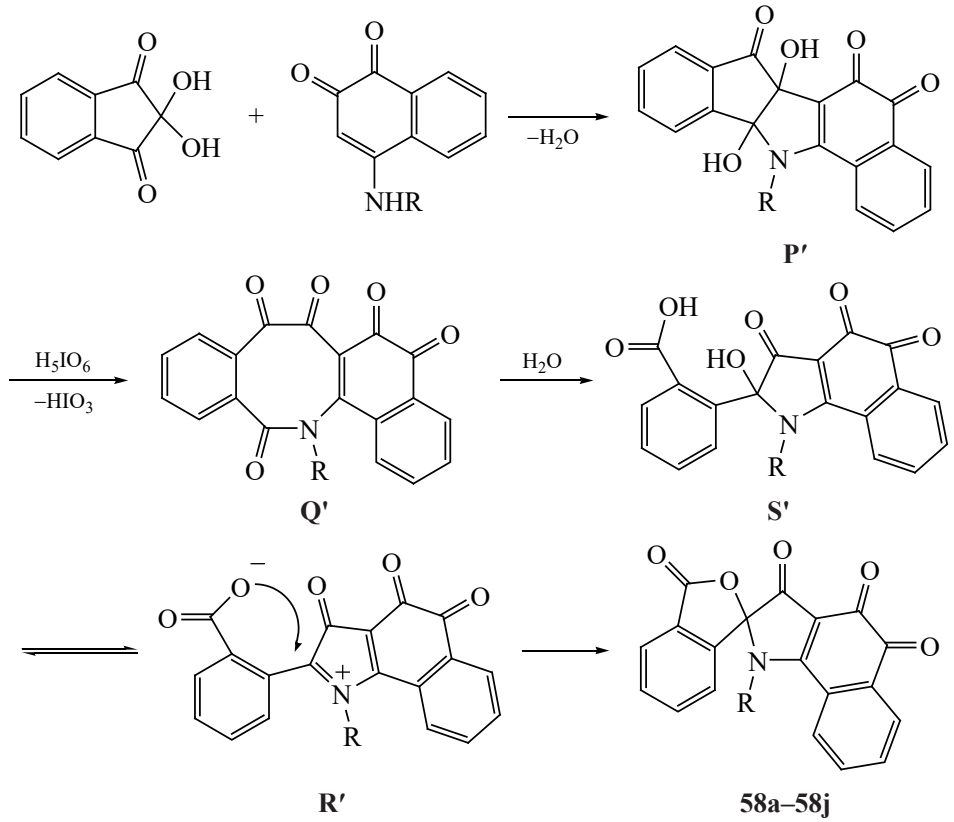
57, R^1 = Ph, R^2 = Me (**a**); R^1 = Bn, R^2 = Me (**b**); R^1 = H, R^2 = Me (**c**); R^1 = Ph, R^2 = H (**d**); R^1 = 4-MeC_6H_4, R^2 = H (**e**); R^1 = 3-ClC_6H_4, R^2 =H (**f**); R^1 = Bn, R^2 = H (**g**); R^1 = *i*-Pr, R^2 = H (**h**); R^1 = $HO(CH_2)_2$, R^2 = H (**i**); R^1 = R^2 = H (**j**).

Scheme 32.



58, R = Ph (**a**), 4-BrC_6H_4 (**b**), 4-IC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 3,5-$(Me)_2C_6H_3$ (**e**), 3-$C_2H_5OC_6H_4$ (**f**), 3-$MeOC_6H_4$ (**g**), 2,5-$(MeO)_2C_6H_3$ (**h**), 4,5-$(Me)_2C_6H_3$ (**i**), 2-MeC_6H_4 (**j**); **59**, R = Ph (**a**), 3,4-$(Me)_2C_6H_3$ (**b**), 4-MeC_6H_4 (**c**), 3,5-$(Me)_2C_6H_3$ (**d**), 1-$CH_2C_{10}H_7$ (**e**), 3,4,5-$(MeO)_3C_6H_2$ (**g**), 4,5-$(Me)_3C_6H_3$ (**h**), Bn (**i**), 2-$ClC_6H_4CH_2$ (**j**).

Scheme 33.



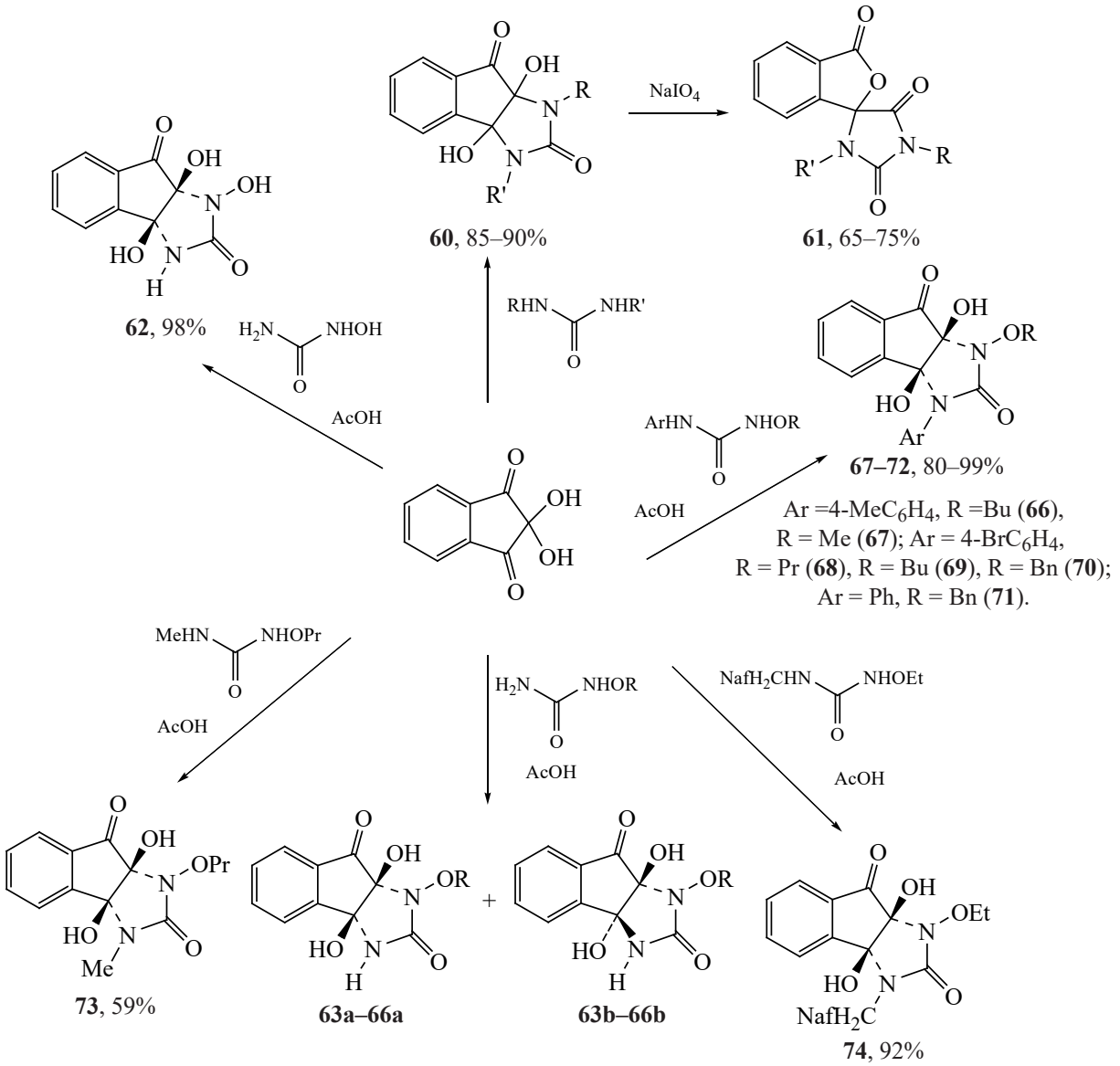
R = Ph, 4-BrC_6H_4, 4-IC_6H_4, 4-MeC_6H_4, 3,5-$(Me)_2C_6H_3$, 3-$OEtC_6H_4$, 3-$OMeC_6H_4$, 2,5-$(Me)_2C_6H_3$, 3,4-$(Me)_2C_6H_3$, 2-MeC_6H_4, CH_2CH_2Ph, pyridin-2-yl.

acid-promoted formation of zwitterionic intermediate **R′**. The necessity of acid conditions for the formation of intermediate products **P′** and **R′** was inferred from the fact that the reaction in acetic acid was complete in a shorter time with higher efficiency.

Ninhydrin reacted with urea and *N*,*N*′-dialkylureas to give adducts **60** which were oxidized with sodium periodate, and spiro hydantoins **61** thus obtained showed anticonvulsant activity [64] (Scheme 34). The reaction of ninhydrin with *N*-hydroxyurea in acetic acid at room temperature afforded 1,3a,8a-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (**62**) as the only *cis*-3a,8a diastereoisomer. 1-Alkoxy-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]-imidazole-2,8-diones **63**–**66** were synthesized in 89–99% yields as mixtures of *cis* (**a**) and *trans* (**b**) diastereoisomers at a ratio of 1:10 by the reaction of *N*-alkoxyureas with ninhydrin in acetic acid (Scheme 34). Conditions were found for the synthesis of *cis* isomers **63a**–**66a** in 67–98% yield [65].

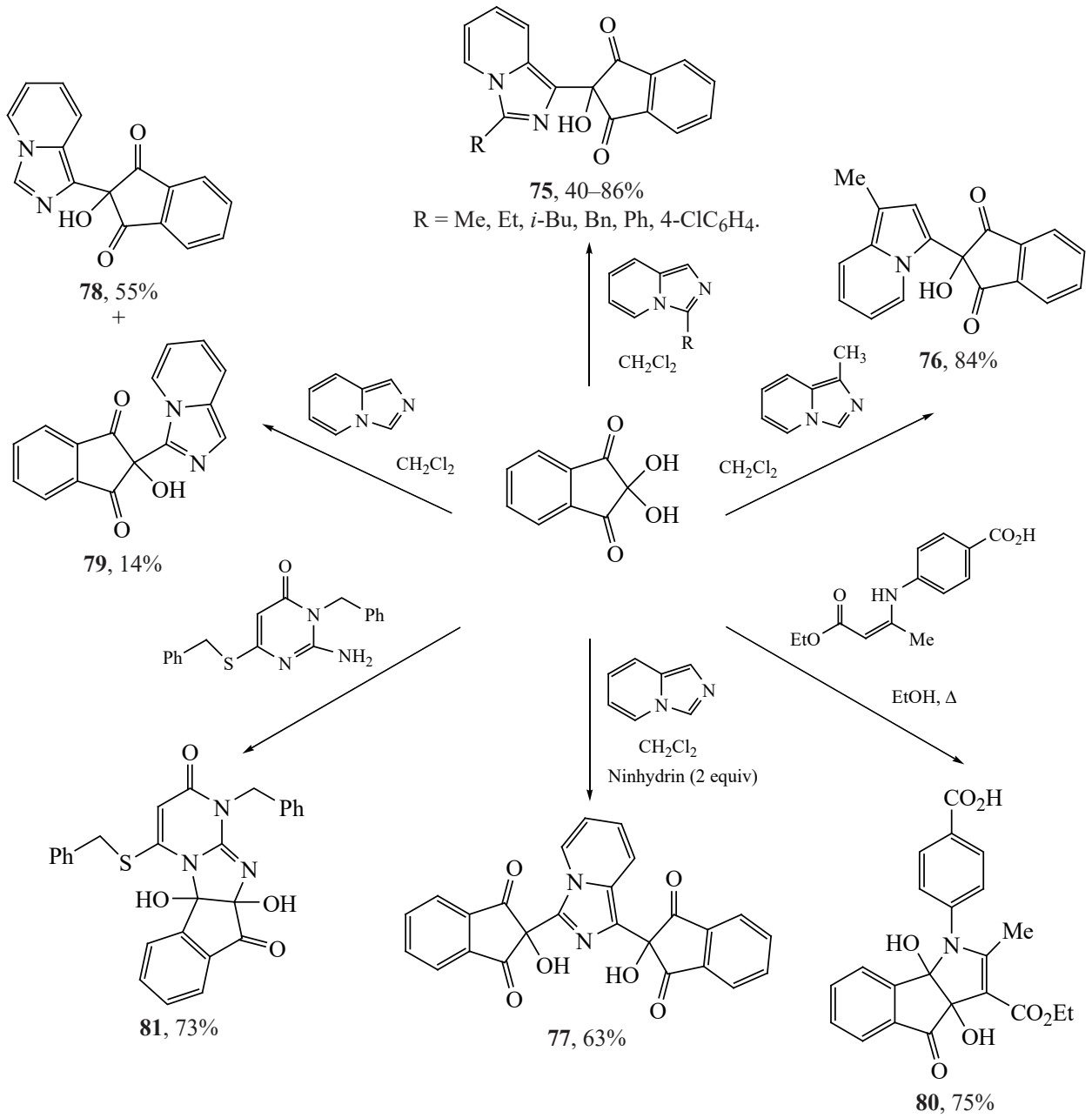
The reaction of ninhydrin with *N*-alkoxy-*N*′-aryl-ureas in acetic acid at room temperature gave only one of the possible diastereoisomers, (2a*S*,8a*R*)-1-alkoxy-3-aryl-2a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno-

Scheme 34.



R = Et, Pr, *cyclo*-C_3H_5, Ph; R' = Ph, 4-EtC_6H_4, 4-$NO_2C_6H_4$, 2-ClC_6H_4, 2-EtC_6H_4, 2,6-$(Et)_2C_6H_3$, 2,4-$(OMe)_2C_6H_3$ (**61**); R = Me (**63**), Et (**64**), *n*-Bu (**65**), Bn (**66**).

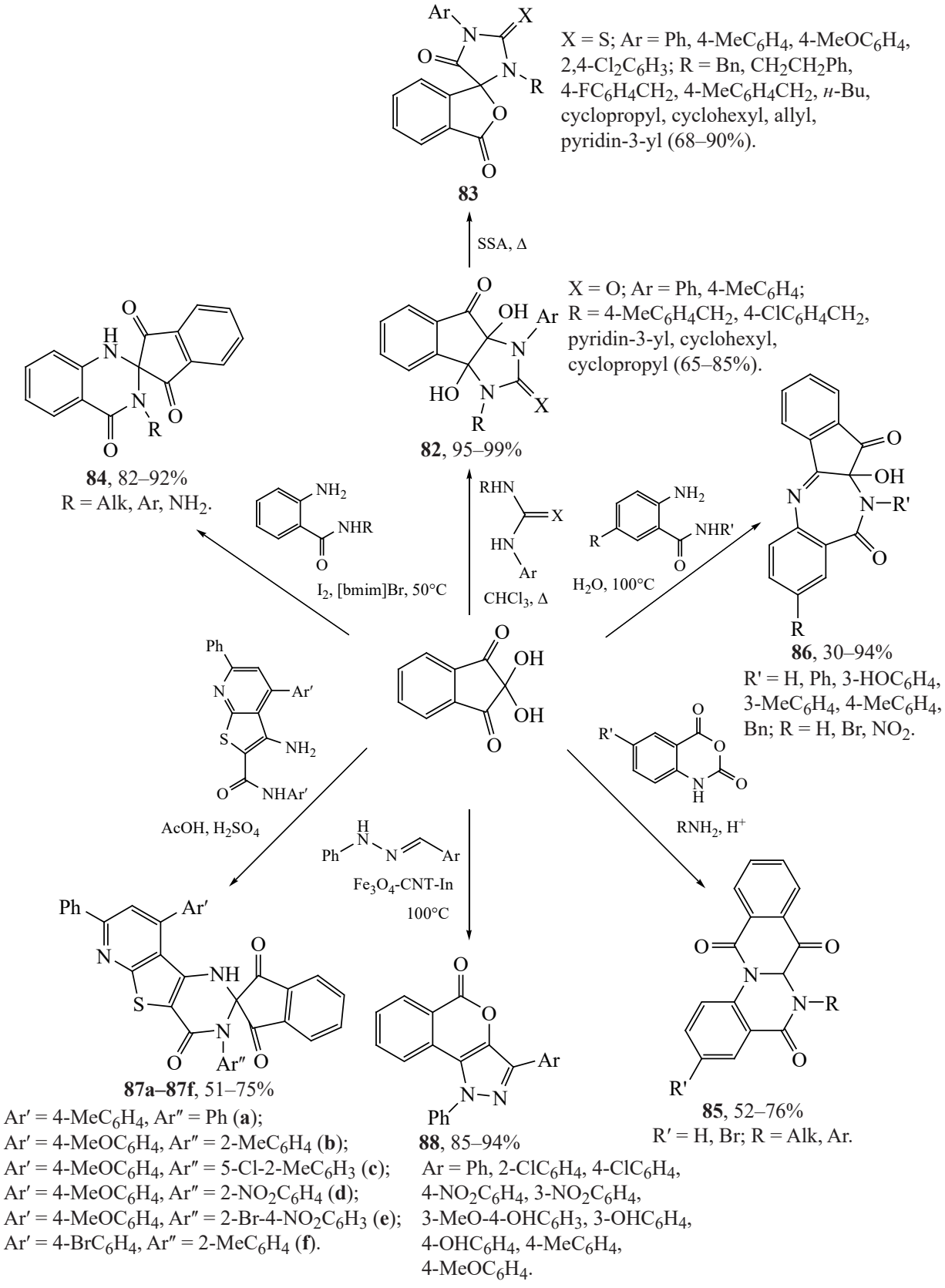
Scheme 35.



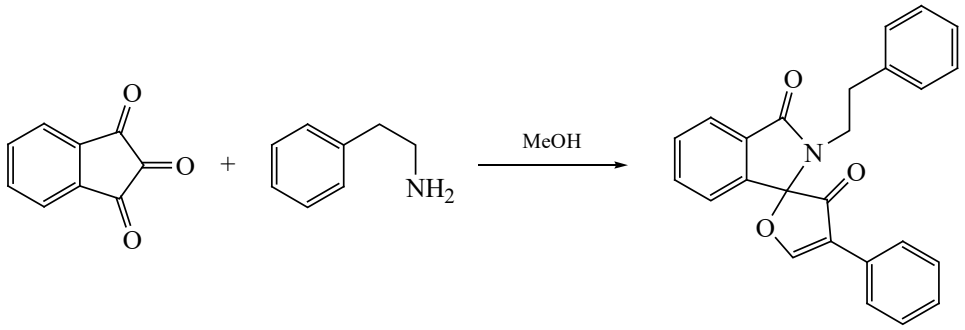
[1,2-*d*]imidazole-2,8-diones **67**–**72** [66] (Scheme 34). Ninhydrin reacted with *N*-methyl-*N*′-propoxyurea under similar conditions to produce (3a*S*,8a*R*)-3a,8a-dihydroxy-3-methyl-1-propoxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (**73**) as a single diastereoisomer. Likewise, 1-ethoxy-3a,8a-dihydroxy-3-(naphthalen-1-ylmethyl)-1,3,3a,8a-tetrahydroindeno-[1,2-*d*]imidazole-2,8-dione (**74**) was obtained with complete diastereoselectivity from ninhydrin and *N*-ethoxy-*N*′-(naphthalen-1-ylmethyl)urea [67] (Scheme 34).

The reaction of ninhydrin with 3-substituted imidazo[1,5-*a*]pyridines involved nucleophilic addition of the C^1 atom of imidazo[1,5-*a*]pyridine to C^2 of ninhydrin with the formation of adducts **75**. Compound **76** was formed in a similar way from 1-methylimidazo-[1,5-*a*]pyridine. Unsubstituted imidazo[1,5-*a*]pyridine reacted with 2 equiv of ninhydrin at room temperature to produce 2,2′-(imidazo[1,5-*a*]pyridine-1,3-diyl)bis-[2-hydroxy-1*H*-indene-1,3(2*H*)dione] (**77**), whereas a mixture of compounds **78** and **79** was formed in a similar reaction with equimolar amounts of the

Scheme 36.


X = S; Ar = Ph, 4-MeC6H4, 4-MeOC6H4, 2,4-Cl2C6H3; R = Bn, CH2CH2Ph, 4-FC6H4CH2, 4-MeC6H4CH2, n-Bu, cyclopropyl, cyclohexyl, allyl, pyridin-3-yl (68–90%).
83
SSA, Δ
X = O; Ar = Ph, 4-MeC6H4; R = 4-MeC6H4CH2, 4-ClC6H4CH2, pyridin-3-yl, cyclohexyl, cyclopropyl (65–85%).
82, 95–99%
84, 82–92%
R = Alk, Ar, NH2.
I2, [bmim]Br, 50°C
CHCl3, Δ
H2O, 100°C
86, 30–94%
R' = H, Ph, 3-HOC6H4, 3-MeC6H4, 4-MeC6H4, Bn; R = H, Br, NO2.
AcOH, H2SO4
Fe3O4-CNT-In
100°C
RNH2, H+
87a–87f, 51–75%
Ar′ = 4-MeC6H4, Ar″ = Ph (a);
Ar′ = 4-MeOC6H4, Ar″ = 2-MeC6H4 (b);
Ar′ = 4-MeOC6H4, Ar″ = 5-Cl-2-MeC6H3 (c);
Ar′ = 4-MeOC6H4, Ar″ = 2-NO2C6H4 (d);
Ar′ = 4-MeOC6H4, Ar″ = 2-Br-4-NO2C6H3 (e);
Ar′ = 4-BrC6H4, Ar″ = 2-MeC6H4 (f).
88, 85–94%
Ar = Ph, 2-ClC6H4, 4-ClC6H4, 4-NO2C6H4, 3-NO2C6H4, 3-MeO-4-OHC6H3, 3-OHC6H4, 4-OHC6H4, 4-MeC6H4, 4-MeOC6H4.
85, 52–76%
R′ = H, Br; R = Alk, Ar.

Scheme 37.



89

reactants [68] (Scheme 35). The reaction of ninhydrin with 4-{[(2*Z*)-4-ethoxy-4-oxobut-2-en-2-yl]amino}-benzoic acid afforded dihydroindeno[1,2-*b*]pyrrole derivative **80** [69]. New polycyclic compound **81** was synthesized in 73% yield by the reaction of ninhydrin with 2-amino-3-benzyl-6-(benzylsulfanyl)pyrimidin-4(3*H*)-one by stirring in DMF for 2 h, followed by addition of water and stirring for 6 h [70] (Scheme 35).

N,*N*′-Substituted ureas and thioureas reacted with ninhydrin to give hemiketals **82** in almost quantitative yield. Compounds **82** underwent oxidative rearrangement to spiro[imidazolidine-4,1′-isobenzofurans] **83** on heating to 65–80°C in the presence of silica sulfuric acid (SiO_2–OSO_3H, SSA) [71] (Scheme 36). Spiro quinazoline derivatives **84** were synthesized from *o*-aminobenzamides and ninhydrin in the presence of a catalytic amount of iodine in ionic liquid [72]. The reaction of isatoic anhydride first with primary amines and then with ninhydrin in dioxane in the presence of HCl at 90–100°C furnished isoquinolino[2,3-*a*]quinazoline-5,7,12-triones **85** [73] (Scheme 36).

The structure of products obtained in the reaction of anthranilamides with ninhydrin in boiling water in the absence of a catalyst was shown to depend on the substituent on the amide nitrogen atom. Anthranilamides having an *ortho* substituent in the *N*-phenyl moiety gave rise to quinazoline derivatives **84**, whereas 11-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*]-[1,4]diazepine-10,12-diones **86** were formed in the other cases [74]. The reaction of ninhydrin with 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxamides in acetic acid in the presence of sulfuric acid produced the corresponding 3′,7′,9′-triaryl-1′*H*-spiro-[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine]-1,3,4′(3′*H*)-triones **87** [75]. Pyrazole-fused isocoumarins **88** were synthesized by the solvent-free reaction of ninhydrin with phenylhydrazones in the presence of a nanocatalyst [76] (Scheme 36).

It was recently shown [77] that the reaction of ninhydrin with 2-phenylethan-1-amine led to the formation of spiro[furan-2,1′-isoindoline] **89** (Scheme 37).

4. CONCLUSIONS

The review shows the importance of ninhydrin as a versatile reagent in organic synthesis, since it provides access to complex cyclic systems via reactions with commercially available starting materials under mild conditions. Various types of ninhydrin adducts, including N-substituted compounds, spiro heterocycles, polycyclic compounds, propellanes, cycloadducts, etc., have been used to create a variety of organic scaffolds. Several examples of stereoselective/asymmetric synthesis have also been demonstrated. The obtained compounds can be used in various branches of industry, many of them are important intermediate products for further synthesis of various organic structures.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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