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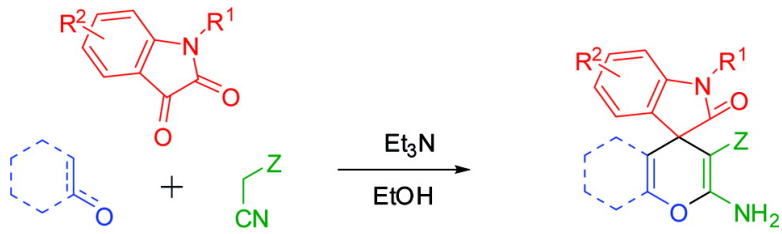

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Versatile Three-Component Procedure for Combinatorial Synthesis of 2-Aminospiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans]

Yuri M. Litvinov, Valery Yu. Mortikov, and Anatoliy M. Shestopalov*

N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Prospect, 119991 Moscow, Russian Federation

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A convenient method of synthesis of substituted and annulated 2-amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] at mild conditions and in good yields is developed. Three component reaction of wide variety of substituted isatins, cyanoacetic acid derivatives, and carbonyl compounds or phenols gives the target compounds. Forty new spiropyrans were obtained, and their structures were proved by elemental analysis and ^{1}H NMR and IR spectral data. It is shown that the use of a not very large set of starting compounds can lead to the synthesis of a thousand-member 2-amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyran] library.

Introduction

Indole and indoline fragments are important moieties of a large number of natural biologically active compunds,[1] and some of indolines, spiro-annulated with heterocycles in the 3-position, have shown high biological activity.[2] Substituted 2-amino-4*H*-pyrans take a significant place among the 6-membered oxygen-containing heterocycles. Some of them possess anticancer and antimicrobial activity;[3,4] others were employed in syntheses of blood anticoagulant warfarin[5] and tacrine analogs (cholinesterase inhibitors).[6] Serotonin receptor modulators (pteropodine **1** and its stereoisomers), natural alkaloids, containing both spiro-indoline and pyran cycles, were isolated from stem bark of *Uncaria tomentosa*[7] (Figure 1).

A lot of spiroheterocycles, containing both indole and pyran heterocycles, spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans], possess anticonvulsant and analgetic,[8] herbicidal,[9] fungicidal,[10,11] and antibacterial[12] activities.

The known method of their synthesis includes a two-step reaction: Knoevenagel condensation to obtain unsaturated nitriles **2** from isatins **3** and cyanoacetic acid derivatives **4** (first step) and interaction of **2** with active α-methylenecarbonyl compounds **5** (second step), which yields the desired 2-amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **6** (Scheme 1).[8−12]

Currently, multicomponent reactions are being rapidly developed[13] because using a "one-pot" methodology makes the synthesis simpler and more environmentally friendly. Recently a one-pot synthesis of different annulated pyranopyrans by reaction of aromatic aldehydes, a cyanoacetic derivative, and kojic acid,[15] 4-hydroxycoumarin,[16,17] or triacetic acid lactone[17] was developed. In addition to aromatic aldehydes, several isatins were introduced into the reaction so that annulated 2′-aminospiro[oxindole-3,4′-((4*H*)-pyrans)] were obtained in high yields.[15−17]

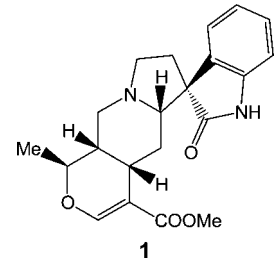

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Figure 1. Natural alkaloid pteropodine.

On the other hand, it is known[13] that the reaction of carbonyl compounds **5** with derivatives of cyanacetyc acid **4** gives 3-cyanopyridine-2(1*H*)-ones **7** and 2,6-dicyanoanilines **8**. Isatins **3** can undergo the Pfitzinger reaction[14] with carbonyl compounds **5** to give quinoline-4-carboxylates **9**, and hydrolysis of the nitrile or ester group can occur with formation of **10** or **11** (Scheme 2).

Recently two papers, describing three-component synthesis of pyrans **6** in aqueous medium with surfactants[18] or solvent-free, catalyzed by $InCl_3$ with microwave assistance,[19] appeared in the literature.

Results and Discussion

In this paper, we describe a versatile synthetic approach to nonannuleted pyrans and 5′,6′,7′,8′-tetrahydrobenzopyrans, benzopyrans, pyrano[3,2-*c*]chromens, and pyrano[2,3-*c*]pyrazols based on a one-pot methodology.

This method, based on three-component Et_3N-catalyzed reaction in ethanol, is the most simple and convenient and would be applicable for the synthesis of different types of annulated and nonannulated 2-amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans].

Recently disclosed three-component methods[18,19] have certain disadvantages. In our attempts to reproduce the technique,[18] we obtained mixtures of pyrans **6** and unsatur-

* To whom correspondence should be addressed. E-mail: shchem@dol.ru.

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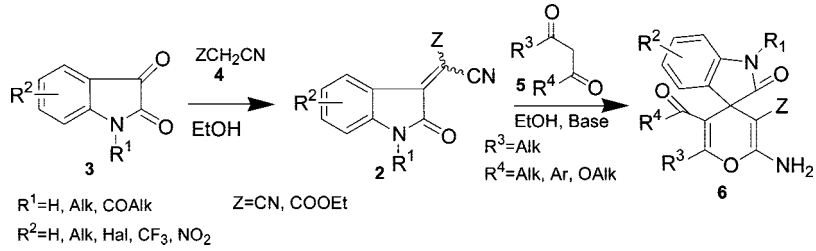
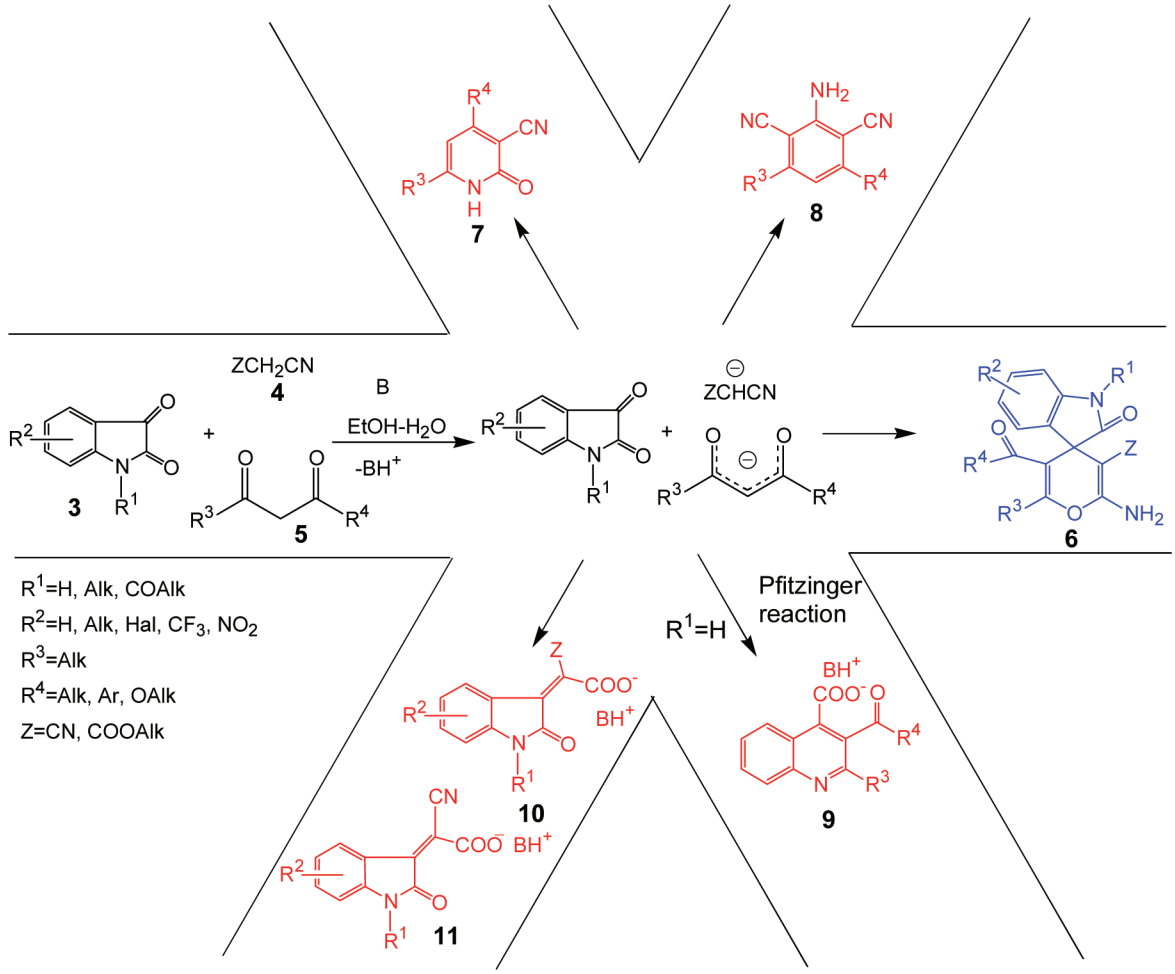
Scheme 1. Two-Step Reaction in the Synthesis of 2-Amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans]



Scheme 2. Three-Component Synthesis of 2-Amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **6** (Blue) and Theoretically Possible By-Products (Red)

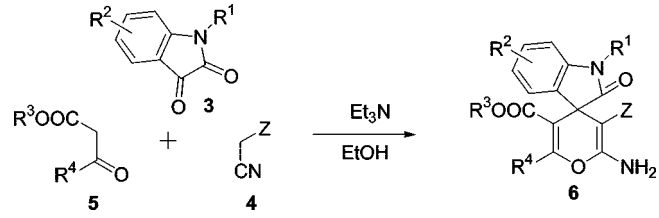


ated nitriles **2**, especially when starting materials contained bulky substituents. This is an evidence of low solubility of nitriles **2** in water. Microwave assistance[19] is not necessary in pyran synthesis because the reactions are slightly exothermic. Moreover, this method requires relatively expensive $InCl_3$ in comparison with more convenient and cheap secondary and tertiary amines, and a complicated workup, requiring large amounts of organic solvents (chromatographic column).

In our method, forty new compounds were obtained in good yield (purity not less 95%) without using complex catalysis[18,19] and irradiations[19] and without additional purification.

To obtain nonannulated 2-amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **6** (Scheme 3), we combined the followng diversity reagents:

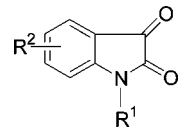
Scheme 3. Three-Component Synthesis of Nonannulated 2-Amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **6**

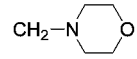


- Substituted isatins **3** (Table 1)
- Cyanoacetic acid derivatives **4** (Figure 2)
- *β*-ketoesters **5** (Table 2).

We used a wide diversity of isatins **3,** both substituted in aromatic nucleus **3**{*2*−*5*} and containing groups with alkyl, ester, carbamoyl, and hydroxymethyl substituents at N-1,

Table 1. Diversity Reagents **3**{*1*−*16*}



Entry	R^1	R^2	Entry	R^1	R^2
1	H	H	*9*	$CH_2C{\equiv}CH$	H
2	H	5-Cl	*10*	CH_2Ph	H
3	H	5-Br	*11*	CH_2COOMe	H
4	H	5-NO_2	*12*	CH_2COOEt	H
5	H	7-Me	*13*	CH_2COOCH_2Ph	H
6	Me	H	*14*	CH_2OH	H
7	Pr^n	H	*15*		H
8	$CH_2CH{=}CH_2$	H	*16*	CH_2CONH_2	H

3{*6*−*16*}. The latter ones were used in spiro[(3′*H*)-indol-3′,4-(4*H*)-pyran] synthesis for the first time.

Reactions proceeded rapidly (5 min in the cases of malononitrile **4**{*1*}, Z = CN, and 30 min in the cases of cyanoactic esters **4**{*2*−*8*}).

The yields ranged from acceptable to excellent, depending on the structure of starting materials. None of the esters, **4**{*2*−*8*} and **5**, underwent re-esterification or hydrolysis.

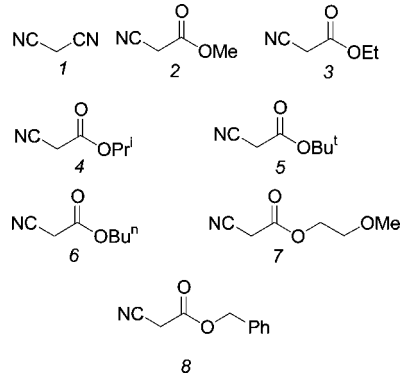
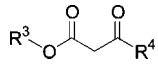


Figure 2. Diversity reagents **4**{*1*−*8*}.

Table 2. Diversity Reagents **5**{*1*−*11*}



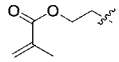
Entry	R^3	R^4	Entry	R^3	R^4
1	Me	Me	*7*	CH_2Ph	Me
2	Et	Me	*8*		Me
3	Pr^i	Me	*9*	Et	Ph
4	Bu^t	Me	*10*	Me	CH_2CO_2Me
5	$CH_2CH{=}CH_2$	Me	*11*	Et	CH_2CO_2Et
6	CH_2CH_2OMe	Me			

Table 3. Nonannulated 2-Amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **6**

entry	mp (°C)	yield (%)
6{*1,3,1*}	243−245	73
6{*3,7,1*}	209−211	65
6{*1,1,3*}	>265[a]	81
6{*2,1,3*}	>265[a]	71
6{*3,1,5*}	>265[a]	53
6{*4,1,5*}	238−240	69
6{*1,4,7*}	213−215	65
6{*1,1,10*}	>265[a]	95
6{*6,2,4*}	221−222	53
6{*6,1,9*}	>265[a]	86
6{*6,6,11*}	135−136	44
6{*7,1,8*}	170−171	45
6{*8,1,1*}	181−183	56
6{*9,3,2*}	154−156	81
6{*9,1,6*}	144−146	41
6{*10,1,1*}	190−192	63
6{*11,1,1*}	222−224	55
6{*11,1,4*}	175−177	47
6{*12,1,3*}	151−153	48
6{*12,2,3*}	179−182	58
6{*14,1,11*}	192−195	49
6{*15,1,10*}	156−158	87

[a] With decomposition.

Yields were relatively low in the cases when one or more of the starting components contained bulky groups (e.g., **6**{*6,6,11*}, **6**{*7,1,8*}, **6**{*9,1,6*}) of esters with bulky alkyl groups. Structure, yields, and melting points of synthesized pyrans **6** are given in Table 3.

Then to expand the scope of three-component method, we substituted cyclic carbonyl compounds and enols **12** for β-ketoesters **5**: β-diketones **12**{*1,2*}, *meta*-aminophenol **12**{*3*}, 4-hydroxycoumarin **12**{*4*}, and 2-pyrazolones **12**{*5*−*8*} (Figure 3).

This made it possible to synthesize a series of annulated heterocycles **13** (Table 4). Despite several active phenols (resorcinol, β-naphtol)[19] were employed in spiro[(3′*H*)-indol-3′,4-(4*H*)-pyran] synthesis, utilization of *meta*-aminophenol **12**{*3*} have not been reported yet.

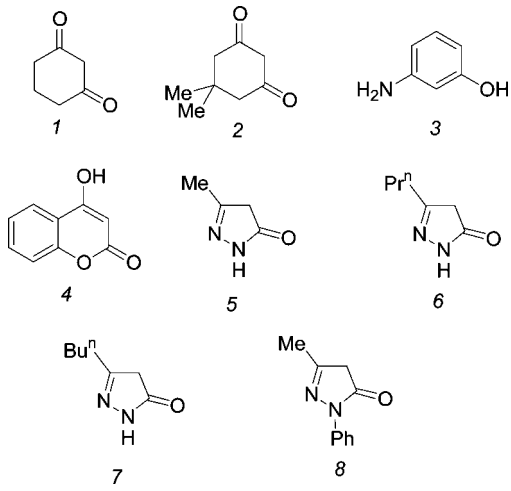
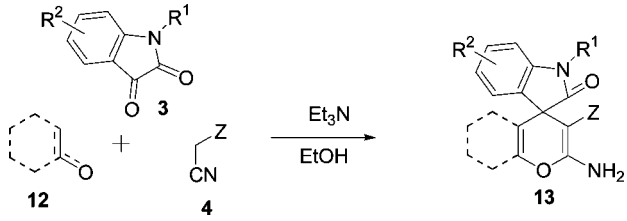


Figure 3. Diversity reagents **12**{*1*−*8*}.

Scheme 4. Three-Component Synthesis of Annulated 2-Amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **13**



The reactions proceeded selectively to give annulated pyrans **13**. The majority of the employed compounds **12** gave rather good yields of pyrans **13** (except cases **13**{*10*,*2*,*2*}, **13**{*11*,*6*,*1*}, **13**{*1*,*3*,*3*}, and **13**{*12*,*3*,*5*}). The carbamoyl group in compound **3**{*16*} did not affect the reaction route, none of the esters underwent reesterification or hydrolysis.

The reported three-component reaction has a general nature: every combination of starting materials **3**, **4**, **5**, or **12** leads to spiropyrans. For example, the set of our starting materials can give a library with total number of (16 isatins **3** × 8 cyanoacetic acid derivatives **4** × 19 methylene-active carbonyl compounds and phenols **5** + **12**) 2432 members.

The selectivity in the synthesis of **6** and **13** can be explained by the strict sequence of reactions in Scheme 5. The most probable solution is that after the simultaneous mixing step isatin **3** undergoes Knoevenagel condensation with highly CH-acidic cyanoacetic ester derivative **4**. We consider this to be so because unsaturated nitriles **2** are formed very easily in the absence of compounds **5** and **12**. Then carbonyl compound **5** or **12** adds to the unsaturated nitrile **2** by Michael reaction, and enolate oxygen attacks nucleophilically nitrile group (Thorpe−Ziegler type reaction). Finally, after the tautomeric proton shift, 2-amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **6** and **13** are formed.

Table 4. Synthesized Annulated 2-Amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans] **13**

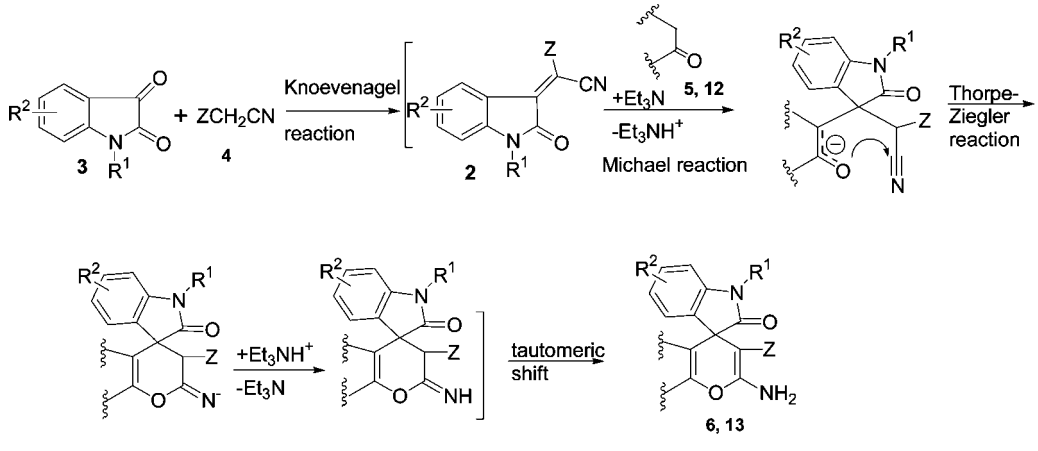
entry	mp (°C)	yield (%)
13{*1*,*8*,*1*}	252−254	52
13{*3*,*5*,*1*}	>265[a]	71
13{*2*,*1*,*1*}	>265[a]	76
13{*8*,*1*,*1*}	252−254	84
13{*10*,*2*,*2*}	261−263	49
13{*11*,*6*,*1*}	215−217	38
13{*12*,*1*,*2*}	242−244	81
13{*13*,*1*,*2*}	224−226	99
13{*15*,*1*,*2*}	207−209	66
13{*1*,*1*,*3*}	>265[a]	68
13{*1*,*3*,*3*}	>265[a]	35
13{*11*,*1*,*4*}	>265[a]	94
13{*16*,*1*,*4*}	>265[a]	84
13{*5*,*1*,*7*}	>265[a]	68
13{*7*,*1*,*6*}	268−270	75
13{*9*,*2*,*5*}	248−251	64
13{*12*,*3*,*5*}	223−225	39
13{*3*,*1*,*8*}	>265[a]	76

[a] With decomposition

Conclusions

We have shown that the use of a wide diversity of substituents in isatins **3** (substitution in aromatic nucleus and at N1), cyanoacetic acid derivatives **4**, and carbonyl compounds **5**, **12**, including aromatic and heterocyclic carbonyl compounds and their tautomers **12**{*3*−*8*} in the three-component reaction makes possible the synthesis of libraries, containing thousands of substituted and annulated 2-amino-spiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans]. The reaction

Scheme 5. Probable Reaction



proceeds in mild conditions. All forty compounds, described in the paper, were synthesized for the first time.

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Supporting Information Available. Experimental procedures, spectroscopic and elemental analysis data for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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