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Facile synthesis of 3-(2-furanyl)indoles via a multicomponent reaction

Chang Sun, Shun-Jun Ji* and Yu Liu

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering Suzhou (Soochow) University, Ren'ai Road, Suzhou Industrial Park, Suzhou 215123, People's Republic of China

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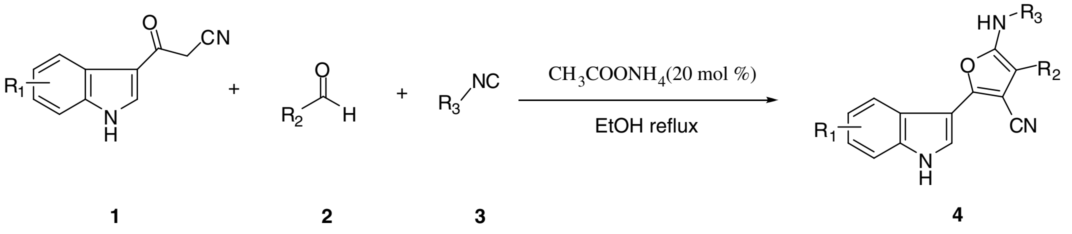
Abstract—3-(2-Furanyl)indoles were firstly synthesized in a one-pot procedure by the reaction of 3-cyanoacetyl indole, aromatic aldehydes and isocyanides in ethanol in the presence of ammonium acetate.

Multicomponent reactions (MCRs), with three or more reactants combine in a one-pot procedure to give a single product, have become increasingly popular during the last decade.[1–7] They are economically and environmentally advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library synthesis, and thus are finding increased use in the discovery process for new drugs and agrochemicals.[8] They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles.[9] MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds.[10,11]

Indole fragment is featured widely in broad ranges of pharmacologically and biologically active compounds.[12] The synthesis and functionalization of indoles has been the object of research for over 100 years. In spite of extensive developments in the chemistry of modified indole and isocyanides, little attention has been paid to the synthesis of 3-(2-furanyl)indoles. To the best of our knowledge, only one procedure was reported in the literature,[13] which was relied on multi-step reactions with yields being low.

In connection with our previous research on indoles,[14] guided by observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably, we investigated a three-component reaction of alkyl isocyanides, 3-cyanoacetyl indole, and aromatic aldehydes in ethanol, which afforded 3-(2-furanyl)indole derivatives in good isolated yields (see Scheme 1). The procedure was simple and easy to handle.

Initially, we carried out the reaction at room temperature without any catalysts only to give the product in



Scheme 1.

Keywords: 3-(2-Furanyl)indoles; Isocyanide; 3-Cyanoacetyl indole; Multicomponent reaction.

* Corresponding author. Fax: +86 512 65880307; e-mail: chemjsj@suda.edu.cn

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Table 1. Optimization of catalysts

Entry	Catalyst	Time (h)	Yield[a] (%)
1	No	4.5	31
2	20% K_2CO_3	1	40
3	20% $NaHCO_3$	1	48
4	10% CH_3COONH_4	1	85
5	20% CH_3COONH_4	1	89
6	30% CH_3COONH_4	1	88

[a] Isolated yields.

Table 2. Optimization of solvents

Entry	Solvent	Time (h)	Yield[a] (%)
1	Ethanol	1	89
2	Toluene	4	22
3	Dichloromethane	1	NR[b]
4	Acetone	1	11

[a] Isolated yields.
[b] No reaction.

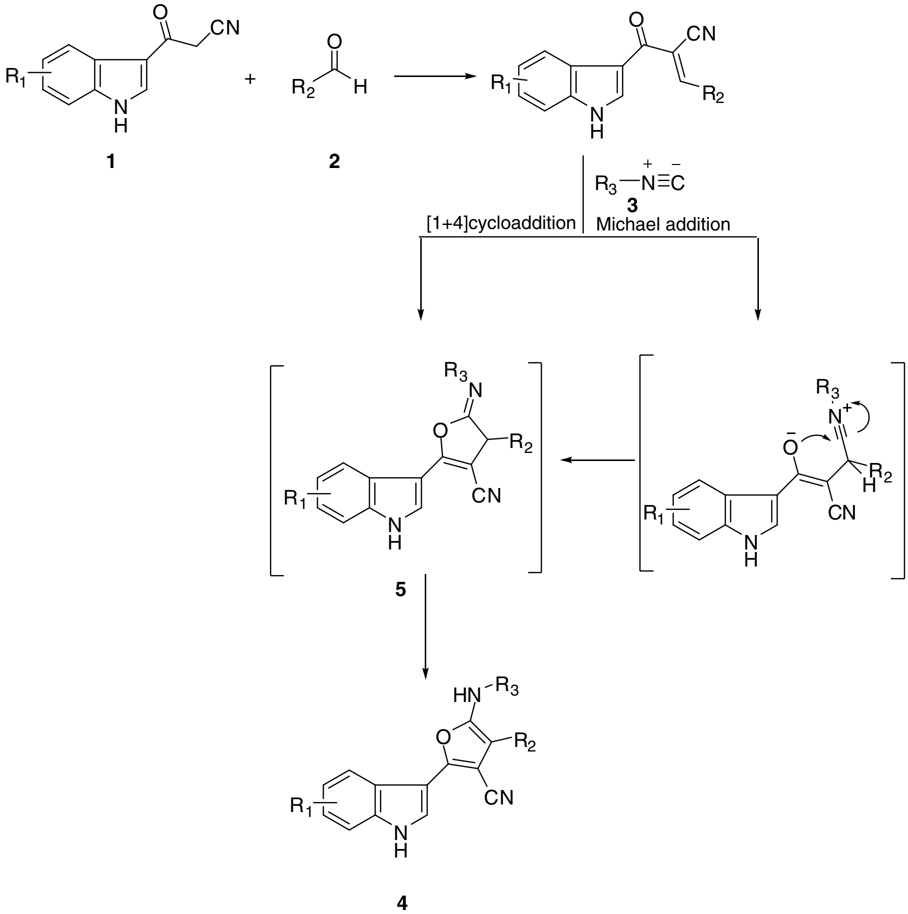
Table 3. Synthesis of compound **4**

Entry	R_1	R_2	R_3	Time (h)	Yield[a] (%)
4a	H	4-ClC_6H_4	*tert*-Butyl	1	89
4b	H	4-$CH_3C_6H_4$	*tert*-Butyl	6	77
4c	H	4-$NO_2C_6H_4$	*tert*-Butyl	1	90
4d	H	3-$NO_2C_6H_4$	*tert*-Butyl	1	87
4e	H	4-FC_6H_4	*tert*-Butyl	1	80
4f	H	4-BrC_6H_4	*tert*-Butyl	1	79
4g	H	2-Pyridyl	Cyclohexyl	5	61
4h	H	4-FC_6H_4	Cyclohexyl	3	68
4i	1-CH_3	4-$NO_2C_6H_4$	*tert*-Butyl	1	79
4j	1-CH_3	3-$NO_2C_6H_4$	*tert*-Butyl	1	76
4k	1-CH_3	2-Pyridyl	*tert*-Butyl	3	70
4l	7-CH_3	4-$NO_2C_6H_4$	*tert*-Butyl	1	91
4m	7-CH_3	3-$NO_2C_6H_4$	*tert*-Butyl	1	87

[a] Isolated yields.

poor yield (Table 1, entry 1). Some bases such as $NaHCO_3$, and K_2CO_3 can push the reaction forward with moderate yields (Table 1, entries 2 and 3). The best result was obtained when ammonium acetate was used, of which the yield was up to 89% (Table 1, entry 5). We also evaluated the amount of catalyst required for this transformation. It was found that when increasing the amount of ammonium acetate from 10 to 20 mol % and 30 mol %, the yields increased from 85% to 89% and 88%, respectively. Using 20 mol % ammonium acetate is sufficient to push the reaction forward. More amounts of the catalyst did not improve yields (Table 1, entry 6).

In addition, we also looked into the solvent effect at reflux condition for this reaction. As showed in Table 2, ethanol gave the most satisfactory result in comparison with other solvents.



Scheme 2. Plausible mechanism for the reaction of isocyanide and aldehyde with 3-cyanoacetyl indole.

Under the optimized reaction conditions, a series of 3-(2-furanyl)indole derivatives **4** were synthesized (Table 3). Interestingly, various substrates such as aryl, and heterocyclic, aldehydes reacted smoothly with isocyanides and 3-cyanoacetyl indole to produce 3-(2-furanyl)indole derivatives in good yields (Table 3, entries **4a**–**m**). The nature of the substitutes on the aromatic ring of the substrates shows some effect on this conversion. Aromatic aldehydes such as nitro-, chloro-, fluoro-, and bromo-derivatives gave higher yields than electron-rich counterparts. The reactions also proceeded efficiently with heterocyclic aldehyde such as 2-pyridylaldehyde. However, we failed to get the expected products when aliphatic aldehydes were used.

Proposed mechanism for the synthesis of 3-(2-furanyl)indole derivative **4** was described in Scheme 2. The formation of these heterocycles can be rationalized by initial formation of a conjugated electron-deficient heterodiene by standard Knoevenagel condensation of the aldehyde **2** and 3-cyanoacetyl indole **1**,[15] followed by a [1+4] cycloaddition reaction or a Michael-type addition reaction with isocyanide **3** to afford an iminolactone **5**, which was then isomerized to yield the 3-(2-furanyl)indoles **4**.

In conclusion, we describe a sequential three-component reaction of aromatic aldehydes, 3-cyanoacetyl indole, and isocyanides for the synthesis of 3-(2-furanyl)indole derivatives.[16] Particularly valuable features of this method include excellent yields of products, shorter reaction time, and easier operation. This reaction realized the modification on the synthesis of 3-(2-furanyl)indole. The new series of 3-(2-furanyl)indole derivatives may provide new classes of biologically active compounds for biomedical screening. This work is currently in progress and the results will be reported in due course.

Acknowledgments

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16. *Typical experimental procedure*: A mixture of 3-cyanoacetyl indole (0.5 mmol), *tert*-butyl isocyanide (0.5 mmol), 4-chlorobenzaldehyde (0.5 mmol) and ammonium acetate (20 mol %) in ethanol (3 mL) was stirred at 78 °C for about an hour. Upon completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The solid was filtered off and recrystallized from ethnol to afford the pure product (**4a**): **5**-(*t-Butylamino)-4-(4-chlorophenyl)-2-(1H-indol-3-yl)furan-3-carbonitrile*. White solid; mp: 241–243 °C; IR (KBr): v 3295 (NH), 2971, 2215 (CN), 1574, 1497 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (s, 9H, CH$_3$), 5.27 (s, 1H, NH), 7.04–8.31 (m, 9H, ArH), 11.87 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1, 54.1, 87.7, 105.2, 109.9, 113.2, 116.8, 120.5, 121.6, 123.4, 124.4, 126.0, 129.3, 130.1, 130.6, 132.2, 136.7, 150.5, 154.5; HRMS [found: m/z 391.1274 (M$^+$), calcd for $C_{23}H_{20}N_3OCl$: M, 391.1265].