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A short synthesis of 3,6-disubstituted *N*-2-thienyl/aryl-indoles

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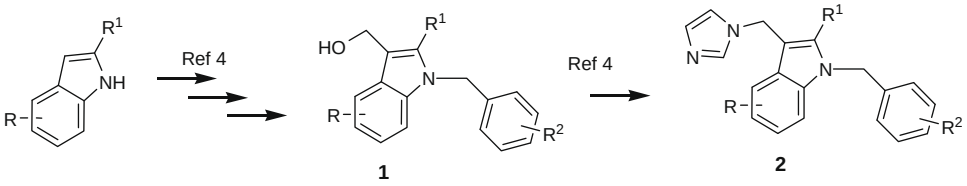
ABSTRACT

A short synthetic strategy for 3,6-disubstituted-*N*-2-thienyl/aryl-indoles, involving reaction of substituted 2,4-difluoro/dichloro-styrene epoxide with substituted 2-formylaminothiophenes or substituted *N*-formylanilines in the presence of a base followed by treatment with an acid, has been developed. The method was applied for the synthesis of a number of indoles with a variety of substituents at 1, 3, and 6 positions of the indole moiety.

Indole ring system is present in many natural products and there are various methods reported for the synthesis of indole framework. The most commonly used method for the construction of indole skeleton is the Fischer indole synthesis discovered in 1883 by Hermann Emil Fischer[1] which involves the reaction of phenyl hydrazine and aldehyde or ketone under acidic conditions. The other important methods include Bischler–Möhlau indole synthesis,[2a] Reissert indole synthesis,[2b,c] Madelung synthesis,[2d] Nenitzescu indole synthesis,[2e,f] Hemetsberger indole synthesis,[2g] Gassman indole synthesis,[2h] Leimgruber–Batcho indole synthesis,[2i] Bartoli indole synthesis,[2j] Larock indole synthesis, and [2k] Fukuyama indole synthesis,[2l] , and the reported methods have been reviewed in many publications.[2m–q] The choice of the method to be used for the particular synthesis depends on the structure of the target molecule, the availability of starting materials, the compatibility of functional groups present in starting material with the reaction conditions, environmental concerns, etc. and a number of new methods or modifications of known methods for the construction of the indole skeleton continue to be reported.[3] The number of publications reporting the synthesis and the applications of various molecules having indole moiety is so large that it becomes difficult to cover all of them. N-Substituted 3-((1*H*-imidazol-1-yl)methyl)-1*H*-indoles of general structure **2** are known to exhibit antifungal activity.[4] These compounds have been prepared from substituted indoles via the intermediates **1** by a series of reactions (Scheme 1).



Scheme 1. Reported synthesis of substituted indoles **2**.

We desired to develop a general method for the synthesis of the compounds with structure **3** wherein the substituted benzyl group in **2** would be replaced with various structural units for the study of the antifungal activity. We envisioned that opening of epoxide **4** with suitable nitrogen nucleophile **5** would give intermediate hydroxy amine **6,** which in turn would react with halogen on aromatic ring in an intramolecular fashion to give the resultant 2,3-dihydro-3-hydroxyindole system **7** as depicted in Scheme 2. Treatment of **7** with an acid would result in dehydration providing

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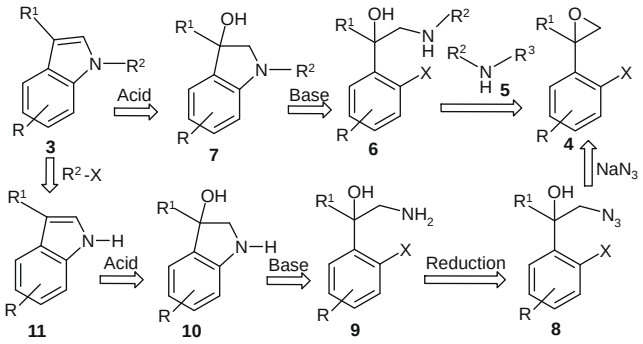


Scheme 2. Retrosynthetic analysis for substituted indoles **3**.

the desired indole moiety **3**. Alternatively, the epoxide **4** could be converted into the haloaminoalcohol **9** via the azide **8** and the indole moiety **11** could be constructed by the treatment of **9** with a base followed by an acid. The indole **11** could then be alkylated[5] to get the desired chemical entities **3**. Our recent efforts in this direction resulted in the development of a method for the synthesis of substituted indoles and the results are presented herein.

Initially, the epoxide **4a**[6] was prepared from 1,3-difluorobenzene as shown in Scheme 3 while the substituted thiophene **5a** was prepared from heptanal by Gewald synthesis[7] followed by formylation. The reaction of epoxide **4a** with substituted thiophene **5a** was attempted under various conditions and it was found that the reaction in the presence of potassium carbonate and tetra-*n*-butylammonium bromide in DMF afforded the alcohol **7a,** which on treatment with dilute hydrochloric acid gave the desired indole **3a**. A number of compounds were prepared[8] to check the generality of the reaction sequence as shown in Table 1.

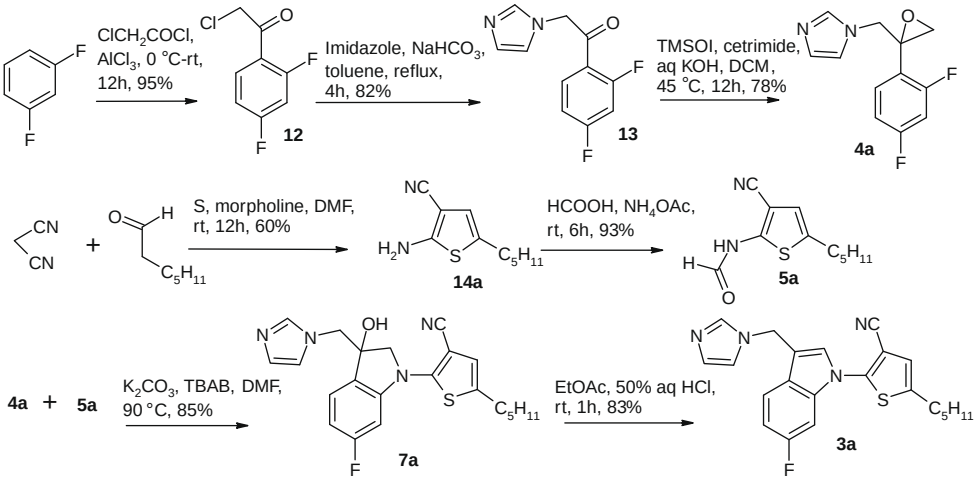
It was observed that the reaction sequence tolerated replacement of imidazole moiety in the epoxide by benzimidazole, benzotriazole, triazole, etc., and the 2,4-difluorophenyl group could be replaced by 2,4-dichlorophenyl group to afford various *N*-2-thienyl-indoles. The epoxides **4** could be reacted with *N*-formyl-4-nitroaniline to generate *N*-aryl-indoles. In the case of *N*-formyl-4-chloroaniline, the intermediate **6** was isolated, which on treatment with potassium *t*-butoxide in DMF followed by the treatment with aq HCl in ethyl acetate afforded the corresponding indole **3i**. Alkyl or cycloalkyl substituents on thiophene ring were also tolerated making the synthetic sequence suitable for generating molecules having varied functionalities.[9] It is noteworthy that this synthetic strategy is also important from the point of the synthesis of highly functionalized indolines **7** which can be used[10] in the synthesis of biologically active compounds and their analogues. It is also noteworthy that Pleixats and co-workers[6c] obtained benzo[*b*]furans from epoxides **4** in the presence of sodium *t*-butoxide in dry DMSO.

The formation of hydroxyindoline **7a** by the condensation of **4a** and **5a** can be rationalized as follows: A proton is abstracted by potassium carbonate, from NH of *N*-formylaminothiophene **5a**, to generate an anion which attacks on epoxide **4a** to open the epoxide ring. The resulting oxyanion might be helping in facile deformylation leading to the formation of anion on nitrogen. This anion subsequently attacks on the carbon atom of the aromatic ring bearing proximal fluorine atom to yield the product **7a** by aromatic nucleophilic substitution. It was observed that *N*-formylamino group was necessary for the reaction to take place wherein formyl group facilitated the formation and stabilization of initial anion. The reaction did not take place in case of the corresponding aminothiophene **14a**.

Alternatively, the synthesis of 3,6-disubstituted indoles **11** was achieved as shown in Scheme 4. The epoxide **4f**[6a–c] was converted into the aminoalcohol **9a** by reaction with sodium azide followed by hydrogenation.[6a] Reaction of the halogenated aminoalcohol **9a** with potassium *t*-butoxide followed by acidic workup afforded the desired substituted indole **11a**. Similarly, the epoxide **4g** prepared from 2,4-dichloroacetophenone was subjected to the reaction sequence as above to afford the 3-methyl-6-chloroindole **11b** in good yields. These indoles **11** could be used as intermediates to prepare analogues of various compounds exhibiting antifungal activity.[11] The substituted indoles **11** could be alkylated[5] by known methods to get the N-substituted indoles **3**.

It was observed that the *N*-2-thienyl-3-hydroxyindolines **7** with imidazolylmethyl substituents were stable while the 3-hydroxyindolines **7** with triazolylmethyl or benzotriazolylmethyl substituents were prone to dehydration, resulting in the corresponding *N*-2-thienylindoles, on silica gel during column chromatography or in solution (the NMR samples kept for a few days showed complete conversion into indoles). In case of *N*-phenylindoles, the intermediate *N*-4-nitrophenyl-3-hydroxy-3-triazolylmethylindole (Table 1, entry 10) was stable while the corresponding intermediate with *N*-4-chlorophenyl substituent (Table 1, entry 9) got readily converted into the substituted indole **3i**. Whenever the indoles **3** were required, the crude products of the reaction of epoxides **4** and the N-formylated amines **5** were directly treated with dil HCl to afford the desired indoles **3** in good yields.[12]

In conclusion, a two-step method for the synthesis of *N*-2-thienyl/aryl-indoles **3** from easily prepared 2-formylaminothiophenes



Scheme 3. Synthesis of 1,3,6-trisubstituted indole **3a**.

Table 1
Synthesis of substituted indoles **3**

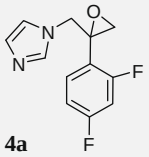
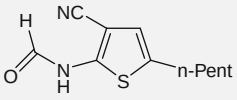
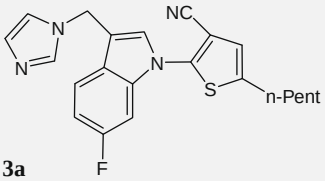
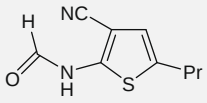
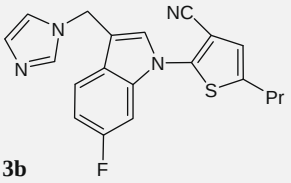
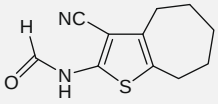
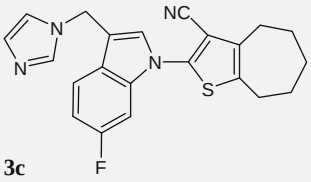
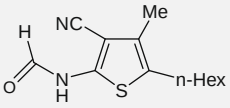
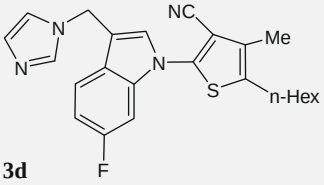
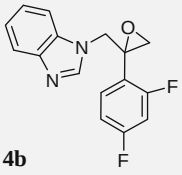
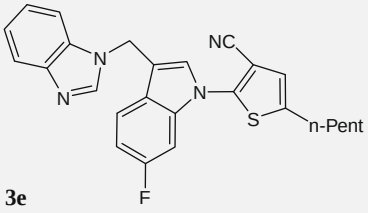
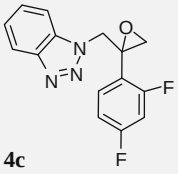
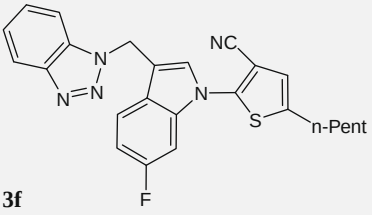
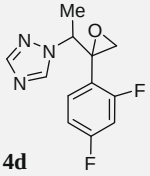
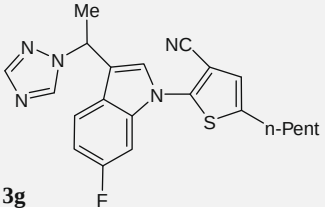
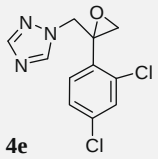
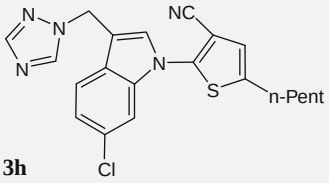
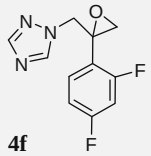
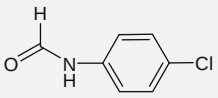
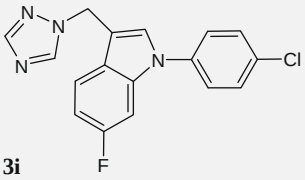
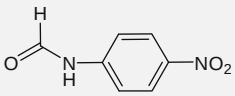
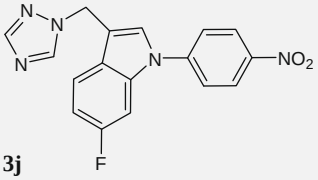
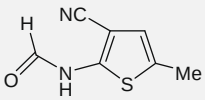
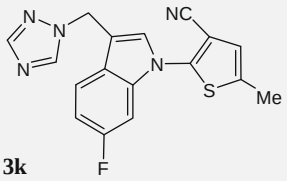
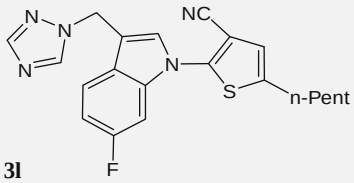
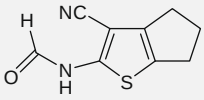
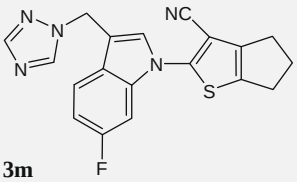
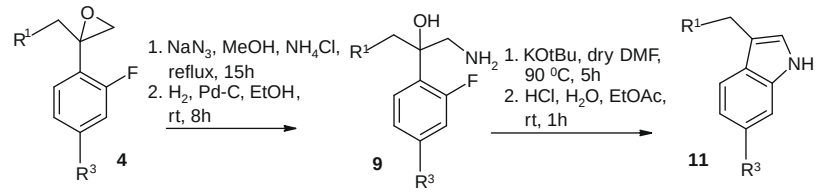
Entry	Reactant **4**	Reactant **5**	Product **3**	Yield[a] (%)
1	 **4a**	 **5a**	 **3a**	70
2	**4a**	 **5b**	 **3b**	65
3	**4a**	 **5c**	 **3c**	57
4	**4a**	 **5d**	 **3d**	62
5	 **4b**	**5a**	 **3e**	63
6	 **4c**	**5a**	 **3f**	84
7	 **4d**	**5a**	 **3g**	80

Table 1 (*continued*)

Entry	Reactant **4**	Reactant **5**	Product **3**	Yield[a] (%)
8	 **4e**	**5a**	 **3h**	58
9	 **4f**	 **5e**	 **3i**	67
10	**4f**	 **5f**	 **3j**	69
11	**4f**	 **5g**	 **3k**	80
12	**4f**	**5a**	 **3l**	84
13	**4f**	 **5h**	 **3m**	82

[a] Isolated yields over two steps.

or *N*-formylanilines **5** and the styrene epoxides **4** has been developed. If required, in some cases, the intermediate *N*-2-thienyl/aryl-3-hydroxyindolines **7** can also be obtained in good yields. The benzotriazole moiety in compounds of the type **3f** could be replaced[11a,13] with different structural units to get various other compounds. The reaction sequence has a potential to generate a



4f : R^1=1,2,4-triazol-1-yl, R^2=R^3=F
4g : R^1=H, R^2=R^3=Cl

9a : R^1=1,2,4-triazol-1-yl, R^2=R^3=F, 82% over 2 steps
9b : R^1=H, R^2=R^3=Cl, 85% over 2 steps

11a : R^1=1,2,4-triazol-1-yl, R^3=F, 85% over 2 steps
11b : R^1=H, R^3=Cl, 56% over 2 steps

Scheme 4. Synthesis of 3,6-disubstituted indoles **11**.

large number of novel indoles and hydroxyindolines with a wide variety of functional groups.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectral data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.049.

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8. Part of this work was presented as a poster during the 11th CRSI National Symposium in Chemistry, NCL, Pune, India, February 6–8, 2009.
9. The new chemical entities prepared in the present work are being checked for biological activity and the results will be published elsewhere.
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12. Procedures and spectral data for all compounds prepared in the present work are available as supplementary data for this Letter. Spectral data for representative compounds: 2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-3-hydroxyindolin-1-yl)-5-pentylthiophene-3-carbonitrile (**7a**): IR (chloroform): 920.12, 1078.66, 1376.81, 1459.25, 1599.50, 2211.65, 2854.24, 2924.60, 3170.32, 3384.61 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, J = 7 Hz, 3H), 1.26–1.42 (m, 4H), 1.57–1.68 (m, 2H), 2.70 (t, J = 7 Hz, 2H), 4.05 (d, J = 12 Hz, 1H), 4.14 (d, J = 12 Hz, 1H), 4.29 (s, 2H), 4.88 (br s, 1H), 6.55 (dt, J = 2, 8 Hz, 1H), 6.67 (s, 1H), 6.75 (dd, J = 2, 10 Hz, 1H), 6.84–7.00 (m, 3H), 7.73 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.9, 22.2, 30.0, 30.6, 31.0, 54.7, 66.1, 98.3 (d, J = 28.18 Hz), 99.0, 108.5 (d, J = 22.68 Hz), 115.2, 121.1, 122.5, 124.9, 125.6 (d, J = 13.91 Hz), 126.6, 126.9, 135.1, 138.3, 147.3, 153.3, 164.4 (d, J = 246.27 Hz). MS (ESI), m/z: 411.5300 (M+1). 2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-pentylthiophene-3-carbonitrile (**3a**): IR (chloroform): 955.79, 1072.29, 1377.00, 1460.65, 1562.43, 1617.97, 2225.06, 2853.64, 2923.78, 3136.32 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.93 (t, J = 7 Hz, 3H), 1.33–1.46 (m, 4H), 1.65–1.80 (m, 2H), 2.83 (t, J = 8 Hz, 2H), 5.43 (s, 2H), 6.91 (s, 1H), 6.99 (dt, J = 2, 8 Hz, 1H), 7.06 (s, 1H), 7.15 (s, 1H), 7.22 (dd, J = 2, 10 Hz, 1H), 7.35–7.41 (m, 2H), 8.19 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.2, 30.1, 30.6, 30.9, 42.7, 98.1 (d, J = 27.66 Hz), 104.5, 111.1 (d, J = 23.85 Hz), 113.5 (2C), 119.4, 120.0 (d, J = 10.49 Hz), 123.5, 126.8, 128.3, 136.5, 137.4, 137.5, 144.3, 145.8, 160.9 (d, J = 243.19 Hz). MS (ESI), m/z: 393.1017 (M+1).
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