

Synthesis of *N*-Aryl Indolines from 2-Fluorobenzaldehyde Dimethylhydrazone Derivatives: Approach to Preparation of C(aryl)-N(Amine) Bond Atropisomeric Amines

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Abstract: 2-(1-indolyl)benzaldehyde dimethylhydrazones are prepared by nucleophilic aromatic substitution of the corresponding 2-fluorobenzaldehyde dimethylhydrazones with lithiated indoline in good yields.

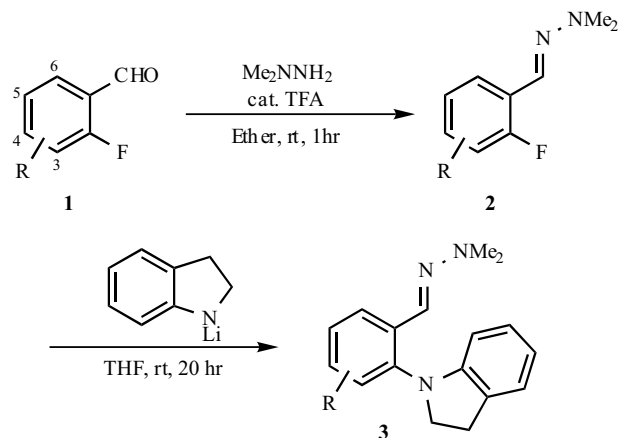
Key words: hydrazone, indoline, nucleophilic aromatic substitution, atropisomer, aminophosphine.

Amines and their derivatives are of fundamental importance as natural products, pharmacological agents, fine chemicals, dyes, and polymers [1]. The presence of the *N*-aryl indoline (2,3-dihydroindole) subunit in a number of synthetically challenging and medically important agents, such as those displaying β_3 adrenergic receptor agonist [2], antipsychotic [3], and analgesic activity [4], has stimulated renewed efforts in the development of methodology for its synthesis. Strategies for constructing *N*-aryl indoline moiety include the reduction of corresponding *N*-aryl indole with cyanoborohydride [5], domino hydroamination-cyclization of halostyrenes [6], copper promoted C-N bond cross-coupling with arylboronic acid [7], KF-alumina promoted C-N bond cross-coupling [8], and nucleophilic aromatic substitution [3,4,9]. Nucleophilic aromatic substitution has been demonstrated to be an effective method for arylating of indoline with *ortho*-fluorobenzamide [3], *ortho*-fluorobenzonitrile [4], and *ortho*-fluorobenzoic acid [9].

On the other hand, hydrazones have been found to be one of the useful synthetic precursors of aldehydes and ketones [10]. To the best of our knowledge, nucleophilic aromatic substitution with *ortho*-fluorobenzaldehyde or its derivatives has never been employed. We tried the nucleophilic aromatic substitution with 2-fluorobenzaldehyde using lithiated indoline; unfortunately, however, the indoline and 2-fluorobenzaldehyde were recovered without our obtaining the corresponding product. Herein, we describe the facile synthesis of *N*-aryl indoline from *ortho*-fluorobenzaldehyde derivatives, such as the corresponding hydrazones (2) with lithiated indoline (Scheme 1).

N-Aryl indolines (3) with various substituents on the aryl ring were easily prepared in two steps from the corresponding 2-fluorobenzaldehydes such as 1. Dimethylhydrazones (2) were prepared from corresponding aldehydes (1) and *N,N*-dimethylhydrazine (DMH) as a protecting reagent with trifluoroacetic acid as a catalyst in good yields (Table 1). We attempted nucleophilic aromatic

substitution with various substituted 2-fluorobenzaldehyde dimethylhydrazones (2) using lithiated indoline [11]. The dimethylhydrazones (2) were converted into the desired *N*-aryl indoline derivatives (3) in moderate to good yields except 2c (Table 1). In the case of 2c with a bulky substituent such as trifluoromethyl at the 3-position, we obtained the corresponding *N*-aryl indoline (3c) in low yield (Entry 3).



Scheme 1

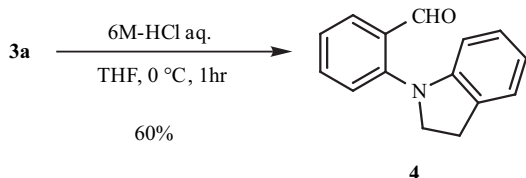
Table 1. Preparation and Nucleophilic Aromatic Substitution of Hydrazone 2

Entry	R	Yield of 2 ^a	Yield of 3 ^a	M.p. of 3
1	H	98 (2a)	84 (3a)	Oil
2	3-F	97 (2b)	92 (3b)	Oil
3	3-CF ₃	87 (2c)	11 (3c)	Oil
4	4-OMe	99 (2d)	66 (3d)	Oil
5	4-Me	96 (2e)	65 (3e)	Oil
6	5-Br	95 (2f)	76 (3f)	103-104 °C
7	6-CF ₃	86 (2g)	72 (3g)	Oil

^a Isolated yields.

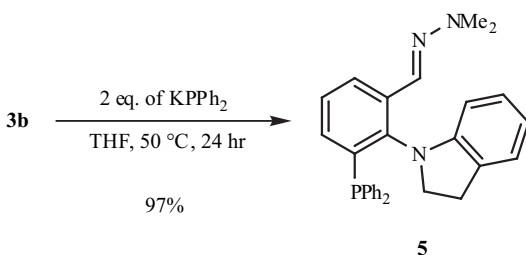
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In addition we investigated the hydrolysis of hydrazones (**3**) for the preparation of *N*-2-formylaryl indoline derivatives such as 2-(1-indolinyl)benzaldehyde (**4**). In the case of **3a**, the corresponding aldehyde (**4**) was found in moderate yield using 6M-hydrochloric acid at 0 °C (Scheme 2) [12, 13].



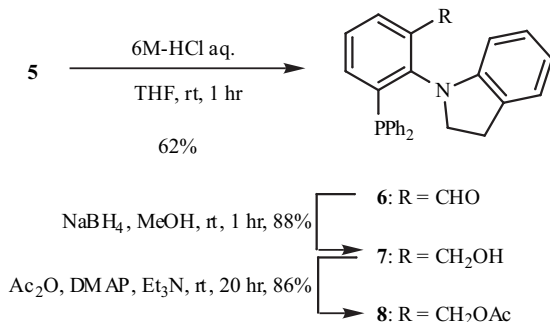
Scheme 2

On the other hand, by using *N*-aryl indoline (**3b**) (R = 3-F) we successfully prepared the aminophosphine hydrazone (**5**) by nucleophilic phosphanylation [14] with KPPH_2 in a 97% yield [15] (Scheme 3).



Scheme 3

Moreover, hydrazone (**5**) was converted into the ester (**8**) as shown in Scheme 4. The corresponding aldehyde (**6**) was obtained by hydrolysis using 6M-hydrochloric acid under argon atmosphere in moderate yield, and the reduction of aldehyde (**6**) with sodium borohydride gave the corresponding alcohol (**7**). This alcohol was converted into the acetate (**8**) [16] using acetic anhydride-triethylamine-DMAP in good yield.

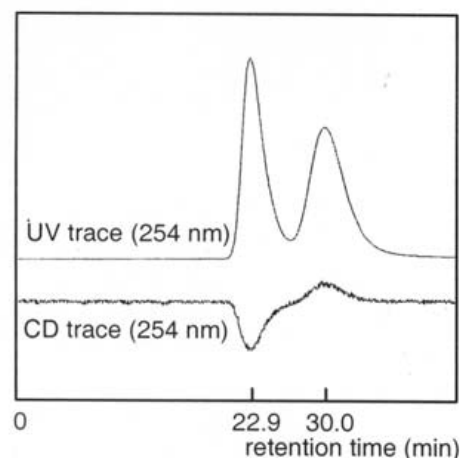


Scheme 4

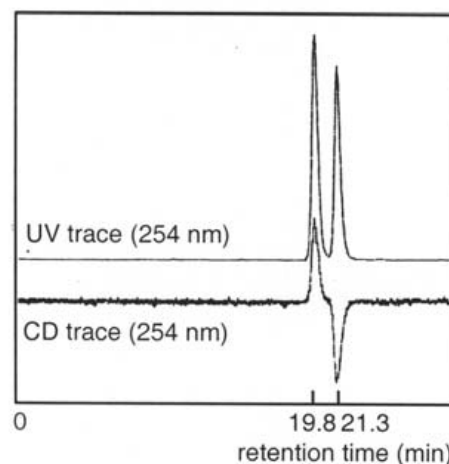
We attempted to separate these atropisomers based on the C(aryl)-N(amine) bond [17] by using HPLC on a chiral phase. We were able to obtain a resolved UV plot for aminophosphines (**5**) (Daicel Chiralcel OJ[®], hexane/ethanol=99:1, 0.3 mL/min) and (**8**) (Daicel Chiralcel OD-H[®], hexane/ethanol=99:1, 0.5 mL/min), in addition to a pair of clear positive and negative CD trace signals (Fig. 1).

In summary, 2-(1-indolinyl)benzaldehyde dimethylhydrazones are easily accessible with nucleophilic aromatic substitution of the corresponding 2-fluorobenzaldehyde dimethylhydrazones. The existence of **5** and **8** as a pair of atropisomers was demonstrated analytically though chiral

phase LC-CD investigations. The enantiomeric resolution and the ability of **5** and **8** for chiral ligands in catalytic asymmetric reaction are currently under investigation and will be reported in due course.



HPLC-CD and UV plot of **5**



HPLC-CD and UV plot of **8**

Fig. (1).

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