1H-INDAZOLES AS SYNTHETIC AUXILIARIES FOR THE SYNTHESIS OF SECONDARY AROMATIC AMINES

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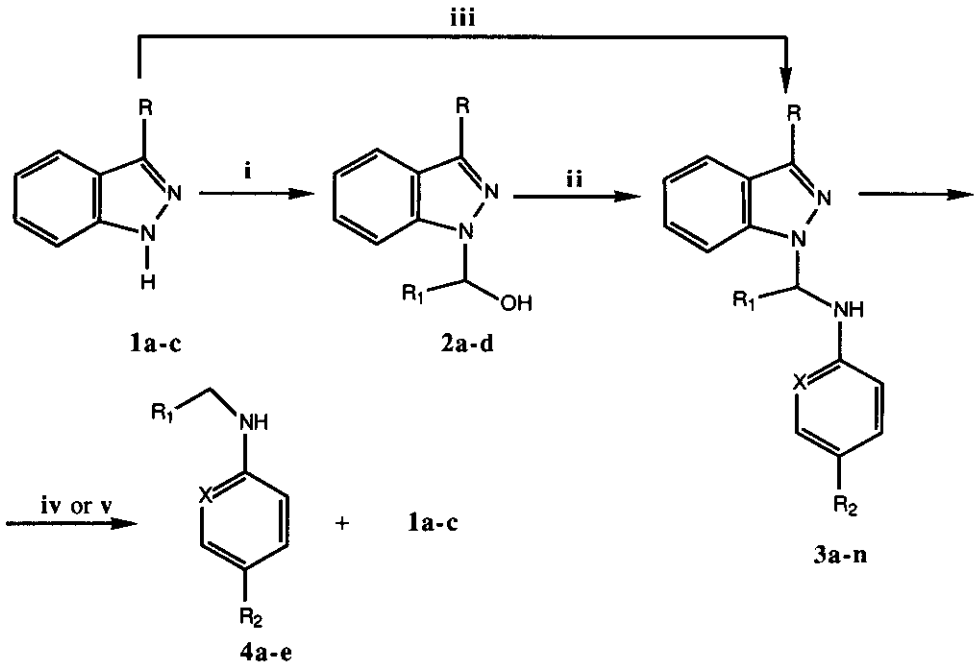
Abstract- Methodology of alkylation of aromatic amines using 1H-indazoles as synthetic auxiliaries is reported.

There are few general procedures for the efficient and selective monoalkylation of primary amines,[1] since the direct alkylation affords very often mixtures. The preparation and subsequent reduction of the corresponding Schiff bases[2] is a frequently followed procedure: the temporary protection of one of the nitrogen positions is another possible approach.
A method for the selective monoalkylation of primary amines by using benzotriazole as synthetic auxiliary has been recently proposed.[3] It seems likely that the high acidity of benzotriazole (pka 8.20)[3b] plays an important role in some steps of the synthetic pathway.
For instance, the last step is the nucleophilic displacement of the benzotriazole moiety by hydrides or Grignard reagents, and the above mentioned acidity of benzotriazole should make the conjugate base of the latter a good leaving group.
In order to assess the properties which must be associated to a synthetic auxiliary in such reactions, we took in consideration the indazole, the C(3) isoster of benzotriazole which is definitely less acidic than the latter (pka 13.8).[4] 1H-Indazoles and aldehydes react readily to give 1-hydroxyalkyl-1H-indazoles which are suitable starting materials for the preparation of Mannich bases,[5] chelating agents,[6] and aminoacids:[7] the easy preparation of these 1-hydroxyalkyl derivatives prompted us to study indazole and some indazole derivatives as synthetic auxiliaries in the alkylation of primary amines. Results of this study are reported here.
1-Hydroxymethyl-1H-indazole (**2a**), 3-methyl-1-hydroxymethyl-1H-indazole (**2b**), 3-carboxymethyl-

1-hydroxymethyl-1H-indazole (**2c**)(Table 1, entry 1), prepared from the corresponding indazoles (**1a-c**) using a modified procedure described by Burckhalter[8] for the synthesis of 1-hydroxymethyl-1H-benzotriazole,[9] and 1-hydroxyethyl-1H-indazole (**2d**) prepared from **1a** using a procedure described by Lopez,[10] were reacted with several aromatic amines and heteroaromatic amine to give the corresponding aminals (**3a-m**) in good yields (Scheme, Table 1, entry 2).

Scheme



i: indazole, aldehyde, boiling ether. ii: amine, boiling ethanol. iii: indazole, propionaldehyde, aniline, ethanol, 25 °C. iv: $LiAlH_4$, ether, 25 °C. For 3b, 3e and 3g also $NaBH_4$, THF, 25 °C. v: allylmagnesium bromide, ether, 25 °C.

Since 1-hydroxypropyl-1H-indazole is described to be unstable at room temperature,[10] we avoided the isolation of the hydroxypropyl derivatives and we obtained the aminal (**3n**) in good yield, allowing to react directly indazole (**1a**), propionaldehyde and aniline at 25°C in ethanol (Scheme, Table, entry 2). The aminals (**3a-f**) and (**3m-n**) were smoothly converted into the corresponding N-alkylamines (**4a-c**) and (**4e-f**) by reduction with $LiAlH_4$ in ether at room temperature in only five minutes (Scheme, Table1, entry 3). The procedure is quite simple and clean, the yields are excellent, and indazoles (**1a-b**) which are produced along with **4** in the reaction could be recovered in large-scale reactions.

This procedure can be extended also to heteroaromatic amines, as in the case of benzotriazole.

entry	compd	R	R_1	R_2	X	yield[a] (%)
1	2a	H	H	-	-	87
	2b	CH_3	H	-	-	85
	2c	CO_2CH_3	H	-	-	89
	2d	H	CH_3	-	-	40
2	3a	H	H	H	CH	76
	3b	H	H	CH_3	CH	79
	3c	H	H	OCH_3	CH	82
	3d	CH_3	H	H	CH	90
	3e	CH_3	H	CH_3	CH	97
	3f	CH_3	H	OCH_3	CH	88
	3g	CO_2CH_3	H	CH_3	CH	87
	3h	CO_2CH_3	H	OCH_3	CH	83
	3i	CO_2CH_3	H	H	N	85
	3l	H	H	H	N	80
	3m	H	CH_3	CH_3	CH	93
	3n	H	C_2H_5	H	CH	93
3[b]	4a	-	H	H	CH	95
	4b	-	H	CH_3	CH	95
	4c	-	H	OCH_3	CH	98
	4d	-	H	H	N	90
	4e	-	C_2H_5	H	CH	91
	4f	-	CH_3	CH_3	CH	85
4	5	-	CH=CH	CH_3	CH	93
	6	-	$CH=CHCH_2$	CH_3	CH	87

Table 1: (a) All compounds were fully characterized by ir, ^{1}H-nmr and ms analyses. (b) The yields are referred to $LiAlH_4$ reductions.

N-Alkylation at the amino group of 2-aminopyridine is very difficult to achieve, due to preferential reaction at the pyridine nitrogen atom to give a quaternary salt. We obtained the alkylation of 2-aminopyridine only at the amino group: in fact $NaBH_4$ reduction of **3i** and $LiAlH_4$ reduction of **3l** afforded the N-2-methylaminopyridine (**4d**) in good yield . In order to evaluate the electronic effect of C-3 substituent on the different ability of indazoles to act as leaving groups, we allowed to react the aminals (**3b**, **3e** and **3g**) under mild reductive conditions ($NaBH_4$, dry THF). The compound (**3g**) reacted completely to give **4b** in 4 h at room temperature; **3b** reacted after 12 h and **3e** was reduced to **4b** in 30% yield only after 10 h at reflux. This data show that the indazole ring increases dramatically its properties of leaving group with C-3 electron-withdrawing substituents, while C-3 electron donor substituents lower it.

In order to evaluate the further synthetic potentiality of the aminals (**3**) we have studied the reactivity of compound (**3e**) with several Grignard reagents; methylmagnesium bromide, vinylmagnesium bromide and allylmagnesium bromide. Under these conditions the 3-methylindazole acts as a leaving group and is displaced by the Grignard nucleophile. The reaction carried out in dry ether gives in good yield N-ethyltoluidine (**4f**)(Scheme, Table 1, entry 3) and the N-alkenyltoluidines (**5** and **6**) in which the terminal double bond is available for transformation into other useful functionalities (Scheme, Table 1, entry 4). It is interesting to note that indazole aminals (**3a-n**) react with $LiAlH_4$ and Grignard reagents (in the case of **3e**) easier than benzotriazole derivatives.[3c,3d] Moreover, carboxymethylindazole aminal (**3g**) reacts faster than benzotriazole derivatives also in the $NaBH_4$ reduction.[6] The data collected show that 1H-indazoles are suitable auxiliaries in the selective alkylation of primary amines. In spite of the lower acidity of indazole as compared to that of benzotriazole, indazoles can be readily displaced from aminals in some instances easier than the benzotriazole.

EXPERIMENTAL

Nmr spectra were recorded on a varian XL 300 (300 MHz) spectrometer and are reported in δ values. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. Microanalyses were performed by C. Erba 1106 analyzer. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer using KBr plates. Mass spectra were recorded on a Kratos MS80 spectrometer. All solvents were ACS reagent grade and were redistilled and dried according to standard procedure. Chromatographic purifications were performed on columns packed with Merck silica gel 60, 230-400 mesh for flash technique.

General procedure for the synthesis of 1-hydroxymethyl-1H-indazoles (**2a-c**)

To a suspension of 25 mmol of the appropriate 1-hydroxymethyl-1H-indazole (**2a-c**) in 10 ml of acetic acid and 10 ml of water, was added with stirring 35% formalin (2 ml, 25 mmol). After 2 h the mixture was diluted with water; the precipitate was filtered off, washed with cold water, and recrystallized from water.

2a: 87%; mp 114-115°C; ir (ν, cm^{-1}) (KBr) 3490, 3220, 1640, 1510; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 5.85 (s, 2H, CH_2), 7.52 (m, 5H); ms$^+$EI (m/z, M^+) 148; Anal. Calcd for $C_8H_8N_2O$: C 64.85, H 5.44, N 18.91. Found: C 64.63, H 6.10, N 17. 28.

2b: 85%; mp 105-106°C; ir (ν, cm^{-1}) (KBr) 3220, 1640, 1510; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.47(s, 3H, CH_3), 5.77 (s, 2H, CH_2), 7.47(m, 4H); ms$^+$EI (m/z, M^+) 162; Anal. Calcd for $C_9H_{10}N_2O$: C 66.65, H 6.21, N 17.27. Found: C 66.34, H 6.17, N 17.22 .

2c: 89%; mp 115-116°C; ir (ν, cm^{-1}) (KBr) 3490, 1715, 1125; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 4.05 (s, 3H, CH_3), 5.91(s, 2H, CH_2), 7.72 (m, 4H); ms$^+$EI (m/z, M^+) 206; Anal. Calcd for $C_{10}H_{10}N_2O_3$: C 58.25, H 4.89, N 13.59. Found : C 58.06, H 4.87, N 13. 67.

General procedure for the synthesis of aminals (**3a-m**)

1-Hydroxymethyl-1H-indazole derivatives (**2a-c**) (10 mmol) and the amine (10 mmol) were dissolved in boiling ethanol (as little as possible) and kept at room temperature for 5 h; most of the product was precipitated. The solid was filtered off, washed with n-hexane and purified by recrystallization from ether/hexane mixtures (Table 1):

3a: 76%; mp 82-84°C; ir (ν, cm^{-1}) ($CHCl_3$) 3500, 3050, 1600, 1500; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 5.75 (m, 2H, CH_2), 6.70-7.16 (m, 10H, CH); ms $^+$EI (m/z, M^+) 223; Anal. Calcd for $C_{14}H_{13}N_3$: C 75.31, H 5.87, N 18.82. Found: C 75.23, H 5.96, N 18.77.

3b: 79%; mp 94-95°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1610, 1520; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.19 (s, 3H, CH_3), 5.73 (m, 2H, CH_2), 6.72-7.71 (m, 8H, CH), 7.99 (s, 1H, CH); ms $^+$EI (m/z, M^+) 237; Anal. Calcd for $C_{15}H_{15}N_3$: C 75.92, H 6.37, N 17.70. Found: C 75.81, H 6.28, N 17.80 .

3c: 82%; mp 69-70°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1600, 1520; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.27 (s, 3H, OCH_3), 5.70 (m, 2H, CH_2), 6.70-7.72 (m, 8H, CH), 8.0 (s, 1H, CH); ms $^+$EI (m/z, M^+) 253; Anal. Calcd for $C_{15}H_{15}N_3O$: C 71.13, H 5.97, N 16.59. Found: C 71.21, H 5.83, N 16.68.

3d: 90%; mp 147-148°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1600, 1500; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.55 (s, 3H, CH_3), 5.67 (m, 2H, CH_2), 6.79-7.70 (m, 9H, CH); ms $^+$EI (m/z, M^+) 237; Anal. Calcd for $C_{15}H_{15}N_3$: C 75.92, H 6.37, N 17.70. Found: C 75.83, H 6.25, N 17.75.

3e: 97%; mp 132-133°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1600, 1500; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.21 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.65 (m, 2H, CH_2), 6.73-7.64 (m, 8H, CH); ms $^+$EI (m/z, M^+) 251; Anal. Calcd for $C_{16}H_{17}N_3$: C 76.46, H 6.82, N 16.72. Found: C 76.33, H 6.71, N 16.68.

3f: 88%; mp 114-115°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1620, 1500; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.54 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 5.61 (m, 2H, CH_2), 6.71-7.60 (m, 8H, CH); ms $^+$EI (m/z, M^+) 267; Anal. Calcd for $C_{16}H_{17}N_3O$: C 71.89, H 6.41, N 15.72. Found: C 71.95, H 6.53, N 15.65.

3g: 87%; mp 128-130°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1710; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.18 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 5.81 (m, 2H, CH_2), 6.68-8.15 (m, 8H, CH); ms $^+$EI (m/z, M^+) 295; Anal. Calcd for $C_{17}H_{17}N_3O_2$: C 69.14, H 5.80, N 14.22. Found: C 69.25, H 5.85, N 14.26.

3h: 83%; mp 118-120°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1710; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.65 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 5.79 (m, 2H, CH_2), 6.80-8.20 (m, 8H, CH); ms $^+$EI (m/z, M^+) 311; Anal. Calcd for $C_{17}H_{17}N_3O_3$: C 65.58, H 5.50, N 13.43. Found: C 65.45, H 5.47, N 13.50.

3i: 85%; mp 158-160°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1720; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 4.09 (s, 3H, OCH_3), 6.00 (m, 2H, CH_2), 7.23-8.22 (m, 7H, CH); ms $^+$EI (m/z, M^+) 250; Anal. Calcd for $C_{15}H_{14}N_4$: C 71.98, H 5.64, N 22.38. Found: C 72.19, H 5.58, N 22.46.

3l: 80%; mp 78-80°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1600, 1510; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 5.10 (m, 2H, CH_2), 6.60-7.80 (m, 7H, CH), 8.05 (s, 1H, CH); ms $^+$EI (m/z, M^+) 224; Anal. Calcd for $C_{13}H_{12}N_4$: C 69.62, H 5.39, N 24.98. Found: C 69.48, H 5.35, N 25.12.

3m: 93%; mp 90-92°C; ir (ν, cm^{-1}) ($CHCl_3$) 3450, 3050, 1600, 1510; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 1.79 (d, J= 6.4 Hz, 3H, CH_3), 6.18 (m, 1H, CH_2), 6.55-7.72 (m, 8H, CH), 8.02 (s, 1H, CH); ms $^+$EI (m/z,

M^+) 251; Anal. Calcd for $C_{16}H_{17}N_3$: C 76.46, H 6.82, N 16.72. Found: C 76.32, H 6.80, N 16.65.

Procedure for the synthesis of aminal (**3n**)

Indazole (**1a**) (1.18 g, 10 mmol), propionaldehyde (0.58 g, 10 mmol) and aniline (0.93 g, 10 mmol) were reacted at room temperature for 5 h; most of the product was precipitated. The solid was filtered off, washed with n-hexane and purified by recrystallization from ether/hexane mixtures (Table 1):
3n: 2.33g, 93%; mp 108-110°C; ir (v, cm^{-1}) ($CHCl_3$) 3450, 3050, 1600, 1510; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 0.83 (t, J= 7.0 Hz, 3H, CH_3), 2.22 (q, J= 7.0 Hz, 2H, CH_2), 5.95 (m, 1H, CH_2), 6.66-7.75 (m, 9H, CH), 8.0 (s, 1H, CH); ms $^+$EI (m/z, M^+) 251; Anal. Calcd for $C_{16}H_{17}N_3$: C 76.46, H 6.82, N 16.72. Found: C 76.38, H 6.89, N 16.76.

Reduction of aminals (**3a-f**) and (**3l-n** by) lithium aluminium hydride: general procedure

To a stirred suspension of lithium aluminium hydride (0.38 g, 10 mmol) in dry THF (10 ml), kept under nitrogen, was added the aminal (**3a-f**) and (**3l-n**) (10 mmol) in dry THF (10 ml). The solution was stirred for 5 min, poured into ice-water, neutralized with 2% HCl, and extracted with ether. The ethereal solution was washed with water, with 5% aqueous sodium carbonate, and then dried ($MgSO_4$). Evaporation of the solvent afforded the amines of purity usually higher than 95% by ^{1}Hnmr. The yields of the amines are reported in Table 1.

Reduction of aminals (**3b. e. g** and **i**) by sodium borohydride: general procedure

Aminals (**3b**, **e**, **g** and **i**) (10 mmol) and sodium borohydride (0.38 g, 10 mmol) were stirred and heated under reflux (if necessary) with dry THF (15 ml) until the reaction was complete. The mixture was poured into ice-water and extracted with ether. The ethereal solution was washed with water, with 5% aqueous sodium carbonate, and then dried ($MgSO_4$). Evaporation of the solvent afforded the amines with a purity similar to that obtained by lithium aluminium hydride reduction.

Reaction of aminal (**3e**) with Grignard reagents: general procedure

To a Grignard reagent (15 mmol) in ether (10 ml) was added, dropwise, the aminal (**3e**) (2.51 g, 10 mmol). The mixture was stirred at 25°C for 30 min and then poured into ice-water. The ethereal solution was washed with water, with 5% aqueous sodium carbonate, and then dried ($MgSO_4$). Evaporation of the solvent afforded the amines of purity usually higher than 95% by ^{1}Hnmr. The yields of the amines are reported in Table 1.

ACNOWLEDGEMENTS

Thanks are due to the Italian MURST for financial support.

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Received, 8th October, 1993