A NOVEL SIMPLE METHOD OF SYNTHESIS OF 2-AMINO-4-(-6-) NITROINDOLES *VIA* BASE PROMOTED CONDENSATION OF *m*-NITROANILINES WITH NITRILES

Nikolai Moskalev and Mieczysław Mąkosza*

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw, Poland

Abstract - Base promoted condensation of nitriles (RCH_2CN) with *m*-nitroanilines at room temperature results in the formation of 3-alkyl- or 3-aryl-2-amino-4-(-6-) nitroindoles. This multistep process includes presumably nucleophilic substitution of hydrogen (or halogen) in the nitroaromatic ring by the nitrile carbanion and subsequent cyclization of the *ortho*-aminophenylacetonitriles so formed to give the aminoindoles.

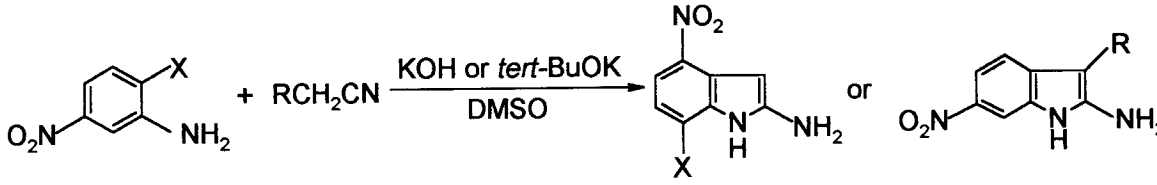
Indole ring system is present in numerous natural products, pharmaceuticals, dyes, etc.[1] Therefore there is a great and continuous interest in methods of the indole ring construction. Although many reactions serving to this purpose are known, only very few approaches are applicable for synthesis of 2-aminoindoles hence they are not readily available. Known methods of direct cyclization into 2-aminoindoles are based on combinations of the Reissert and Pschorr reactions and appear to be laborious procedures.[2] Another methods consist in transformation of 2-indolinethiones [3] or the Beckmann rearrangement of 2-acylindole oximes [4] which should be prepared in advance. Thus, the methods listed above require troublesome syntheses of the starting materials and are of limited practical value.

We have recently reported that substituted nitroindoles can be readily synthesized *via* base induced one-pot reaction of ketones with *m*-nitroaniline (**1a**).[5] This novel indole ring construction process undoubtedly includes oxidative nucleophilic substitution of hydrogen (ONSH) in the nitroaromatic ring with an enolate anion followed by intramolecular condensation of a Baeyer type.

Following this line of research we have found that the reaction of aliphatic nitriles (**2a-c**) and particularly arylacetonitriles (**2d,e**) with *m*-nitroanilines (**1a-c**) gave 2-amino-4- or 6-nitro-3-alkyl or 3-arylindoles

(Table 1). Thus, treatment of *m*-nitroaniline (**1a**) and acetonitrile (**2a**) with KOH in DMSO at room temperature results in a mild exothermic reaction giving 2-amino-4-nitroindole (**3a**) in 50 % yield (entry 1). Similarly, the reaction of **2a** with 2-chloro-5-nitroaniline (**1c**) or even 2-fluoro-5-nitroaniline (**1b**) gives 2-amino-7-chloro-4-nitroindole (**3c**) and 2-amino-7-fluoro-4-nitroindole (**3b**) correspondingly (entries 3 and 2).[6] It should be noted that the reaction of nitrile (**2a**) with **1a-c** gave substances (**3a-c**) resulting from ONSH in the most sterically hindered 2-position of the 3-nitroanilines whereas the products of

Table 1. Reaction of *m*-nitroanilines with various nitriles



1a-c **2a-e** **3a-c** **4b-e**

entry	X, aniline	R, nitrile	Time (h)	Product	Yield (%) [a]
1	H, **1a**	H, **2a**	6	**3a**	50
2	F, **1b**	H, **2a**	0.25	**3b**	28 [b]
3	Cl, **1c**	H, **2a**	12	**3c**	65
4	H, **1a**	Me, **2b**	12	**4b**	32
5	H, **1a**	Et, **2c**	12	**4c**	35
6	H, **1a**	Ph, **2d**	0.5	**4d**	69 [b]
7	F, **1b**	Ph, **2d**	0.5	**4d**	97 [b]
8	Cl, **1c**	Ph, **2d**	0.5	**4d**	95 [b]
9	H, **1a**	1-naphthyl, **2e**	3	**4e**	65

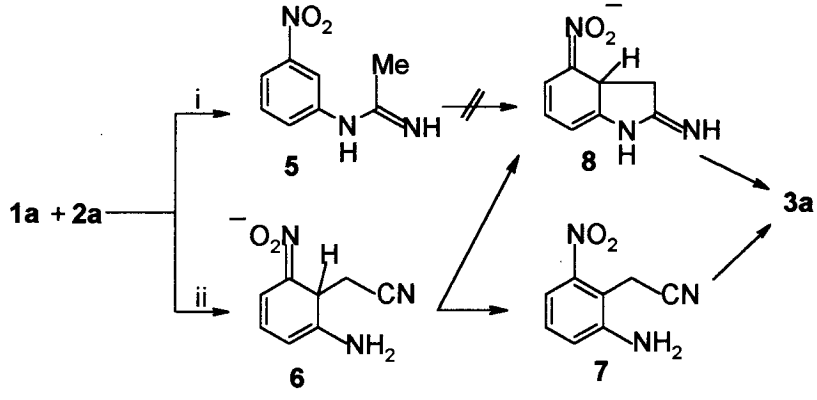
[a]Isolated yields based on **1**. *[b]tert-BuOK was used as the base.*

replacement of the halogens by the nitrile anion were not observed. This type of orientation was observed earlier in other reactions of carbanions with 3-substituted nitrobenzenes. [7] On the other hand, secondary carbanions of nitriles (**2b-e**) in the reaction with **1a-c** form 2-amino-3-alkyl or 3-aryl-6-nitroindoles (**4b-e**) as the result of ONSH (entries 4, 5, 6 and 9) or nucleophilic substitution of halogen (entries 7 and 8) in *para*-position to the nitro group of the anilines. The preference for substitution of Cl over ONSH in **1c** is somewhat surprizing. Perhaps the initial addition of the carbanion occurs in 2-position of 3-nitroanilines (**1b,c**), however further oxidative transformation of the σ^H-adduct so formed is not sufficiently fast.

The formation of 2-aminoindoles when X = H (entries 1, 4, 5, 6 and 9) is obviously a multistep process in which one of the steps should be ONSH by the nitrile carbanion. [8] The reaction can proceed *via* two principal pathways: (i) initial addition of the amino group of **1** to the cyano group of **2** resulting in the formation of amidine (**5**), which upon deprotonation of the methyl group produces σ^H-adduct (**8**) undergoing subsequent intramolecular ONSH to afford 2-aminoindoles; (ii) addition of the nitrile

carbanion to the nitroaromatic ring to give σ^H-anionic intermediate (**6**) followed by its oxidation into *ortho*-aminophenylacetonitrile (**7**) which then enters intramolecular condensation analogous to the Pschorr reaction (Scheme 1). Pathway (i) does not seem feasible due to rather high NH acidity of the amidine moiety. Moreover, both nitriles (**2a** and **2d**) did not form amidines when aniline was taken as a substrate in place of *m*-nitroanilines under the same conditions. This supposition can be supported by observation that *m*-nitroacetanilide does not form 4- (or 6-) nitro-2-oxindole under the similar reaction conditions, whereas its *N*-methylated derivative cyclizes into 1-methyl-4-nitro-2-oxindole in good yield. So far we are

Scheme 1



not able to make a choice in favor of one of the two intermediates (**7** and **8**) on the route (ii), however, similar as for the reaction of **1a** with ketones we suppose that the stabilization of the σ^H-anionic intermediate(**6**)through intramolecular interaction between the amino and the cyano group can play an important role. [5]

The obtained 2-aminoindoles (**3**, **4**) [9] are stable crystalline solids (except **4b** and **4c** are not stable in solution) and can be dried at 60°C on the air. However, they did not show sharp mp because of decomposition at elevated temperatures.

This new method of indole synthesis offers a very simple and efficient access to the important class of indole derivatives which otherwice are hard available.

REFERENCES

This paper is dedicated to professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

1. J. Bergman, 'Studies in Natural Products Chemistry,' Vol. 1, Part A, ed. by A. Rahman, Elsevier, New York, 1988, pp.3 - 30; K. S. J. Staplefold, 'Rodd's Chemistry of Carbon Compounds, Vol. 4, Part B ed. by S. Coffey, Elsevier, 1977, pp. 63 - 163; A. P. Kozikowski, *Heterocycles*, 1981, **16**, 267; M. Somei, K. Kizu, M. Kumimoto, and F. Yamada, *Chem. Pharm. Bull.*, 1985, **33**, 3696.
2. A. N. Kost, R. S. Sagitullin, V. I. Gorbunov, and N. N. Modianov, *Khim. Geterotsikl. Soed.* (Rus.), 1973, N 3, 359; F. Troxler, 'The Chemistry of Heterocyclic Compounds,' Vol. 25 (2), ed. by A. Weissberger and E. C. Taylor, J. Willey & Sons Inc., New York, 1972, pp. 197 – 199.

3. T. Hino, M. Nakagawa, T. Hashizume, N. Yamaji, and Y. Miwa, *Tetrahedron*, 1971, **27**, 775.
4. A. S. Bailey, C. J. Barnes, and P. A. Wilkinson, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1321; J. B. Hester Jr., *J. Org. Chem.*, 1970, **35**, 875; J. Kebrle and K. Hoffman, *Helv. Chim. Acta*, 1956, **39**, 116.
5. N. Moskalev and M. Mąkosza, *Tetrahedron Lett.*, 1999, in print.
6. *General procedure.* To a solution of **2** (5 - 10 mmol) and powdered KOH or *tert*-BuOK (10 - 40 mmol) in 15 - 30 mL of DMSO **1** (1 - 5 mmol) was added in one portion. The deep colored mixture was stirred at room temperature for 0.25 - 12 h, poured in 100 - 300 mL of cold water, extracted with EtOAc , and the extract was dried with $MgSO_4$ and the product (**3** or **4**) was isolated using preparative TLC or column chromatography (SiO_2, Et_2O). Substance (**4d**) produced in the reactions of **1b** and **1c** needed no chromatographical purification.
7. M. Mąkosza, T. Glinka, and A. Kinowski, *Tetrahedron*, 1984, **40**, 1863; M. Mąkosza and J. Winarski, *Acc. Chem. Res.*, 1987, **20**, 282.
8. O. N. Chupakhin, V. N. Charushin, and H. C. van der Plas, 'Nucleophilic Aromatic Substitution of Hydrogen,' Academic Press, 1994, pp. 33 - 41; M. Hamana, G. Iwasaki, and S. Saeki, *Heterocycles*, 1982, **17**, 177; G. Iwasaki, K. Wada, S. Saeki, and M. Hamana, *Heterocycles*, 1984, **22**, 1811; M. Mąkosza, *Russ. Chem. Bull.*, 1996, **45**, 331; M. Mąkosza and K. Stalinski, *Polish J. Chem.*, 1999, **73**, 151.
9. *Characterization data.* **3a**: dark reddish-green crystals (EtOAc - Et_2O) mp 229 - 230 °C (decomp); ^1H NMR (DMSO-d_6) δ 6.04 (dd, 1H, H-3, J = 0.8 and 2.1 Hz), 6.47 (br s 1H, *NH*$_2$), 6.74 (dd, 1H, H-6, J = 7.4 and 7.4 Hz), 7.31 (1H, H-7, J = 0.9 and 7.4 Hz), 7.76 (dd, 1H, H-5, J = 0.9 and 7.4 Hz), 10.85 (br s, 1H, *NH*). MS m/z (rel. int) 177 (M^+, 100), 160 (18), 147 (12), 131 (44). *Anal.* Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 54.44; H, 3.81; N, 23.77.
3b: dark red crystals (EtOAc - Et_2O) mp 230 - 233 °C (decomp); ^1H NMR (DMSO-d_6) δ 6.08 (d, 1H, 3-H, J = 3.4 Hz), 6.47 (s, 2H, *NH*$_2$), 6.65 (dd, 1H, H-6, J = 9.2 and 9.3 Hz), 7.28 (dd, 1H, H-5, J = 9.2 and 9.2 Hz), 11.41 (br s, 1H, *NH*). MS m/z (rel. int) 195 (M^+, 100), 165 (26), 149 (60). *Anal.* Calcd for $C_8H_6N_3O_2F$: C, 49.23; H, 3.08; N, 21.54. Found: C, 49.44; H, 3.16; N, 21.78.
3c: dark red crystals (EtOAc - Et_2O) mp 228 - 231 °C (decomp); ^1H NMR (DMSO-d_6) δ 6.07 (d, 1H, H-3, J = 2.0 Hz), 6.42 (s, 1H, *NH*$_2$), 6.78 (d, 1H, H-6, J = 8.9 Hz), 7.76 (d, 1H, H-5, J = 8.9 Hz) 11.22 (s, 1H, *NH*). MS m/z (rel. int) 213, 211 (M^+ 32, 100), 183 (5), 181 (16), 167 (17), 165 (50). *Anal.* Calcd for $C_8H_6N_3O_2Cl$: C, 45.40; H, 2.84; N, 19.86. Found: C, 45.29; H, 2.88; N, 20.08.
4b: dark red crystals (EtOAc - Et_2O) mp 216 - 220 °C (decomp); ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H, *Me*), 6.28 (s, 2H, *NH*$_2$), 6.99 (d, 1H, H-4, J = 8.7 Hz), 7.74 (dd, 1H, H-5, J = 2.1 and 8.8 Hz), 7.89 (d, 1H, H-7, J = 2.1 Hz), 10.62 (s, 1H, *NH*). MS m/z (rel. int) 191 (M^+, 100), 161 (33), 145 (64). *Anal.* Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.99. Found: C, 56.69; H, 4.61; N, 21.82.
4c: dark red crystals (EtOAc - Et_2O) mp 180 - 183 °C (decomp); ^1H NMR (DMSO-d_6) δ 1.08 (t, 3H, *Me*, J = 7.5 Hz), 6.28 (s, 2H, *NH*$_2$), 7.04 (d, 1H, H-4, J = 8.9 Hz), 7.73 (dd, 1H, H-5, J = 2.1 and 8.9 Hz), 7.90 (d, 1H, H-7, J = 2.1 Hz), 10.60 (s, 1H, *NH*). MS m/z (rel. int) 205 (M^+, 48), 190 (100), 144 (47). *Anal.* Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.37; N, 20.48. Found: C, 58.38; H, 5.23; N, 20.60.
4d: dark green crystals (toluene) mp 240 - 242 °C (decomp); ^1H NMR (DMSO-d_6) δ 6.49 (s, 2H, *NH*$_2$), 7.25 - 7.50 (m, 5H, *Ph*), 7.31 (d, 1H, H-4, J = 8.9 Hz), 7.81 (dd, 1H, H-5, J = 2.2 and 8.9 Hz), 8.09 (d, 1H, H-7, J = 2.2 Hz), 10.90 (s, 1H, *NH*). MS m/z (rel. int) 253 (M^+, 100), 223 (20), 207 (42). *Anal.* Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.35; N, 16.60. Found: C, 66.31; H, 4.20; N, 16.42.
4e: dark red crystals (EtOAc - Et_2O) mp 233 - 236 °C (decomp); ^1H NMR (DMSO-d_6) δ 6.25 (s, 1H, *NH*$_2$), 6.71 (d 1H, H-4, J = 8.9 Hz), 7.38 - 7.75 (m, 7H, *1-naphthyl*), 7.74 (dd, 1H, H-5, J = 2.2 and 8.9 Hz), 8.09 (d, 1H, H-7, J = 2.2 Hz), 11.00 (s, 1H, *NH*). MS m/z (rel. int) 303 (M^+, 100), 273 (31), 257 (37), 128 (18). *Anal.* Calcd for $C_{18}H_{13}N_3O_2$: C, 71.29; H, 4.29; N, 13.86. Found: C, 71.20; H, 4.13; N, 13.65.

Received, 28th April, 1999