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INTERACTION OF (1-PHENYLETHYL)INDOLE-2-CARBONITRILE WITH C-NUCLEOPHILES

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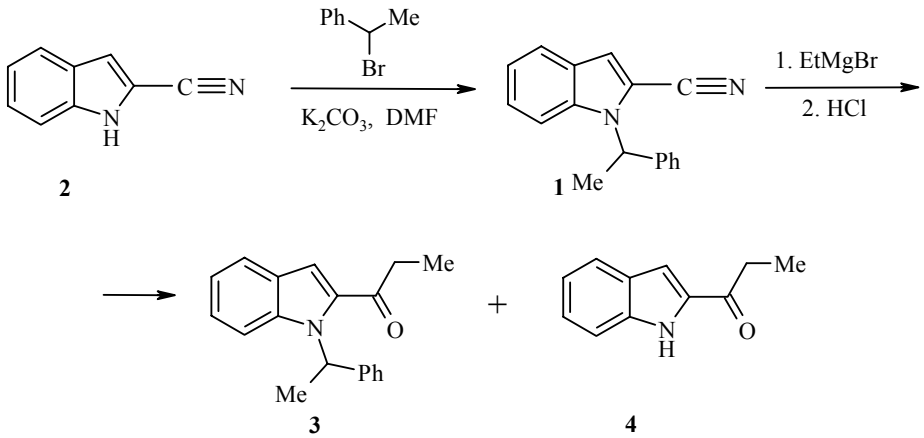
Methods of obtaining ketones and enamino esters have been developed on the basis of reactions of 1-(1-phenylethyl)indole-2-carbonitrile with organomagnesium and organozinc compounds. Removal of a benzyl group from the indole nitrogen atom by the Grignard reagent has been discovered.

Keywords: enamino esters, 2-propionylindole, 1-(1-phenylethyl)indole-2-carbonitrile, [1-(1-phenylethyl)-2-indolyl]-1-propanone, ethyl ester of *Z*-3-amino-3-[1-(1-phenylethyl)-2-indolyl]acrylic acid, Blaise reaction, interactions with C-nucleophiles, N-dibenzylation.

We have already reported the use of 2-cyanoindole in the synthesis of indole derivatives with a chiral substituent on the nitrogen atom [1, 2]. In the present work, with the aim of studying the synthetic potential of 1-(1-phenylethyl)indole-2-carbonitrile, we have investigated its interaction with such C-nucleophiles as organomagnesium and organozinc compounds. Previously the interaction was described of 1-methyl- and 1-phenylsulfonylindole-2-carbonitriles with organolithium compounds and with methylmagnesium chloride [3], which led to the formation of indole ketones in good yield, while in the case of 1-phenylsulfonylindole-2-carbonitrile partial removal of the phenylsulfonyl group occurred.

To obtain 1-(1-phenylethyl)indole-2-carbonitrile (**1**) we used the alkylation of 2-cyanoindole (**2**) with 1-phenylethyl bromide in the presence of potassium carbonate in DMF at 40-50°C. Elimination predominates at higher temperatures.



2 **1** **3** **4**

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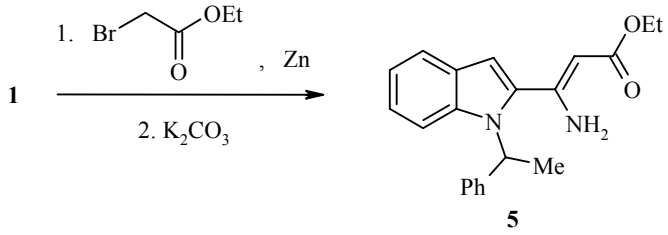
The interaction of nitrile **1** with ethylmagnesium bromide in boiling ether leads to the formation of a mixture of [1-(1-phenylethyl)-1-indolyl]propan-1-one (**3**) and 2-propionylindole (**4**). On carrying out the reaction in benzene [4] compound **4** remains the main reaction product. The usual conditions for removing a benzyl group from an indole nitrogen atom are the use of $AlCl_3$ in benzene [5] or Na in liquid ammonia [6]. The use of potassium *tert*-butylate in the presence of oxygen has been described [7]. Removal of an N-benzyl group from indole on interaction with an excess of methyllithium for a long time is known [8]. It is assumed that the process occurs through preliminary fission of a benzyl proton, which involves the formation of a carbene and indolyl anion as a result of α-elimination. Since addition of Grignard reagents to a nitrile proceeds slowly, especially in the presence of steric difficulties, it may be proposed that ethylmagnesium bromide is capable of initiating removal of an N-benzyl substituent in the indole molecule as a result of the competing detachment of a benzyl proton of the substituent. Copper(1) salts are capable of catalyzing addition of Grignard reagents to nitriles [9]. The interaction of compound **2** with ethylmagnesium bromide on boiling in THF in the presence of CuCN leads to ketone **3** in high yield and, according to data of mass spectrometry, the formation of the debenzylation product **4** was not observed. Variation of the conditions of reacting nitrile **1** with ethylmagnesium bromide may therefore direct the process to form the N-benzylated indole ketone **3** or 2-acylindole **4** unsubstituted at the indole nitrogen atom.

We then studied the possibility of using nitrile **1** for the synthesis of enamino esters (other promising synthons in the indole series) on interaction with organozinc compounds obtained *in situ* under the conditions of the Blaise reaction [10]. Activation of the process with ultrasound has been described to obtain higher yields of enamino esters [11], but gave no results in our case, while the use of zinc dust, previously treated with dilute hydrochloric acid, enabled enaminoester **5** to be obtained in good yield. We assign compound **5** to the *Z*-configuration, since it is known that similar enaminoesters exist preferentially as *Z*-isomers [10]. The results of the investigations carried out are given in Table 1.



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We have therefore shown the possibility of using indole-2-carbonitrile containing a chiral substituent at the nitrogen atom for obtaining promising synthons of the indole series on interaction with C-nucleophiles. Conditions were found leading to minimum detachment of the benzylic proton from the substituent at the indole nitrogen atom.

TABLE 1. Interaction of Nitrile **1** with C-Nucleophiles

Reagent	Conditions	Product	Yield, %
EtMgBr	Et_2O	**3**	33
		4	6
EtMgBr	PhH	**4**	48
EtMgBr	CuCN, TTF	**3**	82
$BrZnCH_2COOEt$	Zn, TTF	**5**	75

EXPERIMENTAL

The IR spectra were obtained on a UR 20 instrument for nujol suspensions or pure compounds. Chromato-mass spectral investigation of reaction mixtures and isolated compounds was carried out using a Carlo Erba/Kratos Fractovap Series 4200 gas-liquid chromatograph, column Ultra 1, Hewlett-Packard, 25 m × 0.2 mm, thickness of phase layer 0.33 μm, carrier gas helium (1 ml/min), flow divider 1:10, evaporator temperature 280°C, temperature gradient from 150 to 280°C (5°C/min). Mass spectral detector was an ITD 700 (Finnigan MAT), ionization by electron impact 70 eV, mass range *m/z* 45-400. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker MS 400 (400 and 100 MHz respectively) in $CDCl_3$, internal standard was TMS. Melting points were measured in open capillaries, values given are not corrected. A check on the progress of reactions and the purity of isolated compounds was effected by TLC on Silufol UV 254 plates. All solvents were purified by the standard procedure [12].

1-(1-Phenylethyl)indole-2-carbonitrile (1). Potassium carbonate (4.9 g, 34 mmol) and 1-phenylethyl bromide (6.3 g, 34 mmol) were added to a solution of 2-cyanoindole (4.4 g, 31 mmol) in DMF (30 ml) and the mixture was stirred at 40-50°C for 6 h. Water (150 ml) was then added to the reaction mixture, which was extracted with ether (3 × 50 ml). The extract was washed with water (5 × 50 ml), with saturated NaCl solution (50 ml), and dried with anhydrous Na_2SO_4. The solvent was distilled off in vacuum, the residue was chromatographed on a column of silica gel, eluting with a mixture of ethyl acetate–petroleum ether, 1:50. Yield 6.4 g (84%). The ^{1}H NMR spectrum corresponded with the data published previously in [2].

Interaction of 1-(1-Phenylethyl)indole-2-carbonitrile (1) with Ethylmagnesium Bromide. A. A solution of compound **1** (0.5 g, 2 mmol) in THF (2 ml) was added to a solution of ethylmagnesium bromide obtained from magnesium (50 mg, 2.1 mmol) and ethyl bromide (0.23 g, 2.1 mmol) in THF (5 ml) in an atmosphere of Ar, and straightaway CuCN (3.6 mg, 0.04 mmol) was added. The reaction mixture was boiled for 4 h, cooled, 15% hydrochloric acid (5 ml) was added, the mixture boiled for 2 h, and extracted with ether (50 ml). The extract was washed with water, with saturated NaCl solution, and dried over anhydrous sodium sulfate. The solvent was removed in vacuum, and the residue chromatographed on silica gel, eluting with a mixture of ethyl acetate–petroleum ether, 1:50. Compound **3** (0.45 g, 82%) was obtained as a viscous oil, which crystallized on standing. IR spectrum, ν, cm^{-1}: 705 (C_6H_5), 740, 765, 800, 1670 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 1.98 (3H, d, *J* = 7.2, $CHC\underline{H}_3$); 3.12 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 7.02 (1H, m, H arom.); 7.08-7.37 (8H, m, $C\underline{H}CH_3$ + H arom.); 7.42 (1H, s, H-3); 7.72 (1H, m, H arom.). ^{13}C NMR spectrum, δ, ppm: 9.04; 18.07; 33.64; 53.18; 112.36; 113.81; 120.53; 122.94; 125.21; 126.37 (2C); 126.77; 126.85; 128.43 (2C); 134.81; 138.38; 141.67; 195.38 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 277 (18) $[M]^+$, 173 (50), 144 (47). 105 (100), 77 (12). Found, %: C 82.50; H 7.12. $C_{19}H_{19}NO$. Calculated, %: C 82.28; H 6.90.

B. A solution of compound **1** (0.5 g, 2 mmol) in benzene (5 ml) was added to a solution of ethylmagnesium bromide, obtained from magnesium (72 mg, 3 mmol) and ethyl bromide (0.33 g, 3 mmol) in ether (5 ml) in an atmosphere of argon. The ether was then distilled off, and the reaction mixture boiled for 4 h. The mixture was cooled, 15% hydrochloric acid (5 ml) was added, the mixture boiled for 2 h, and extracted with ether (50 ml). The extract was washed with water, with saturated NaCl solution, and dried over anhydrous sodium sulfate. The solvent was removed in vacuum, and the residue chromatographed on silica gel, eluting with a mixture of ethyl acetate–petroleum ether, 1:20. 2-Propionylindole (**4**) (166 mg, 48%) was obtained with mp 152°C (from benzene) (lit. mp 153-154.5°C [13]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 3.03 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 7.19 (1H, t, *J* = 8.0, H arom.); 7.24 (1H, s, H-3); 7.38 (1H, t, *J* = 8.0, H arom.); 7.47 (1H, d, *J* = 8.1, H arom.); 7.74 (1H, d, *J* = 8.0, H arom.); 9.4 (1H, br. s, NH).

C. A solution of compound **1** (0.5 g, 2 mmol) in ether (5 ml) was added to a solution of ethylmagnesium bromide, obtained from magnesium (50 mg, 2.1 mmol) and ethyl bromide (0.23 g, 2.1 mmol). The reaction mixture was boiled for 6 h, cooled, water (3 ml) and conc. HCl (0.4 ml) were added, the mixture boiled for 2 h, and extracted with ether (50 ml). The extract was washed with water, with saturated NaCl solution, and dried

over anhydrous sodium sulfate. The solvent was removed in vacuum, and the residue chromatographed on silica gel, eluting with ethyl acetate–petroleum ether, 1:50). Compound **3** (0.18 g, 33%) and compound **4** (20 mg, 6%) were obtained.

Ethyl Ester of *Z*-3-Amino-3-[1-(1-phenylethyl)-2-indolyl]acrylic Acid (5). Zinc dust was activated by washing with 3 N HCl, then 3 times with distilled water, 3 times with alcohol, and dried in vacuum. Several drops of ethyl bromoacetate were added to a suspension of activated zinc dust (4.6 g, 71 mmol) in THF (15 ml) in an atmosphere of Ar, then heated until reaction began. A solution of nitrile **1** (3.5 g, 14 mmol) in THF (15 ml) was added in one portion, then with gentle boiling a solution of ethyl bromoacetate (9.5 g, 57 mmol) in THF (15 ml) was added dropwise during 30 min. The reaction mixture was boiled for 30 min, cooled, THF (100 ml) was added, then 50% K_2CO_3 solution (20 ml), the mixture stirred for 30 min, the organic layer was separated, and the aqueous layer extracted with THF (20 ml). The extract was dried with anhydrous magnesium sulfate, the solvent removed in vacuum, the residue was chromatographed on silica gel, eluting with a mixture of ethyl acetate–petroleum ether, 1:25. Yield was 3.6 g (75%). IR spectrum, ν, cm^{-1}: 705, 710, 755, 765, 800, 1620, 1670 (C=O), 3330, and 3470 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.96 (3H, d, *J* = 7.1, $CHC\underline{H}_3$); 4.20 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.98 (1H, s, C=CH); 6.11 (1H, q, *J* = 7.1, $C\underline{H}CH_3$); 6.78 (1H, s, H-3); 7.00 (1H, d, *J* = 8.2, H arom.); 7.03-7.15 (2H, m, H arom.); 7.20-7.40 (7H, m, H arom. + NH_2); 7.65 (1H, d, *J* = 7.7, H arom.). ^{13}C NMR spectrum, δ, ppm: 14.59; 18.84; 54.09; 59.18; 87.48; 104.12; 113.27; 120.34; 121.51; 122.69; 126.07 (2C); 127.25; 128.37; 128.78 (2C); 136.74; 137.82; 141.27, 152.59; 169.99 (C=O). Found, %: C 75.88; H 6.80. $C_{21}H_{22}N_2O_2$. Calculated, %: C 75.42; H 6.63.

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