Preparation of 2-Acylaminobenzonitriles from 3-Hydroxyimino-3*H*-indoles

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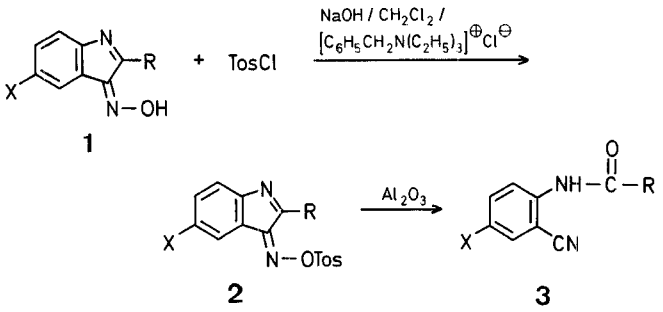
2-Aminobenzonitrile derivatives are important starting materials in the synthesis of a wide range of products of pharmacological interest such as quinazolines[1,2,3], benzodiazepines[4], and 2-aminobenzophenones[5].

Among the different reagents that have been applied to the Beckmann rearrangement of oximes[6], the decomposition of their *O*-tosyl derivatives on alumina[7,8] is a good method[8] that has not been further used. We report a simple method for the synthesis of 2-acylaminobenzonitriles **3** based on the Beckmann fragmentation[6,9] of 3-hydroxyimino-3*H*-indoles **1**. We have found that 3-hydroxyimino-3*H*-indoles **1** can be transformed into the corresponding *O*-tosyl derivatives **2** under solid-liquid phase-transfer-catalysed conditions[10] using sodium hydroxide and catalytic amounts of benzyltriethylammonium chloride in dichloromethane and also under liquid-liquid conditions using a 40% aqueous solution of sodium hydroxide. When the compounds **2**, are chromatographed on basic or acidic alumina, they undergo (similarly to α-ketoximes) the Beckmann fragmentation to give 2-acylaminobenzonitriles **3** in good yields (Table).



1,2,3	a	b	c	d	e	f
R	CH_3					
X	H	H	F	Cl	NO_2	H

The 3-hydroxyimino-2-aryl(heteroaryl)-3*H*-indoles **1b**[11], **1c** (m.p. 289 °C dec.), **1d**[12], **1e** (m.p. 299 °C dec.), and **1f**[13] were prepared by nitrosation with sodium nitrite in concentrated acetic acid from the corresponding 2-aryl(heteroaryl)-indoles[14]. For **1a**, isopentyl nitrite in ethanol solution was used as the nitrosating agent[15].

Basic alumina: Alumina (100 g, Merck 0.063–0.200 mm) is shaken for 2 h with an aqueous 50% solution of sodium hydroxide (2.5 ml)[16].

Acid alumina: Alumina (100 g, Merck 0.063–0.200 mm) is shaken for 2 h with an aqueous (1 : 1) solution of hydrochloric acid (2.5 ml).

2-Acylaminobenzonitriles 3; General Procedure:

A solution of tosyl chloride (2.29 g, 0.012 mol) in dichloromethane (35 ml) is added dropwise to a stirred mixture of the 3-hydroxyimino-3*H*-indole **1** (0.01 mol), sodium hydroxide (1 g, 0.025 mol), and benzyltriethylammonium chloride (114 mg, 0.5 mmol) in dichloromethane (65 ml). The mixture is stirred at room temperature for 2 h, filtered, and the solvent removed under reduced pressure to give the crude *O*-tosylindole derivative **2**. This product is chromatographed on basic or acidic alumina (100 g) and elution with hexane containing an increasing proportion of chloroform and finally with 1 : 1 chloroform/methanol yields the 2-acylaminobenzonitriles **3**. Special care must be taken with these products (in particular the halocompounds **3c** and **3d**) because they are rather volatile and can be lost by concentration in vacuum.

Table. 2-Acylaminobenzonitriles **3** from 3-Hydroxyimino-3*H*-indoles **1**

Product	Yield[a] [%]	m.p.[b] [°C]	Molecular formula[c] or m.p. [°C] reported	I.R. (KBr)[d] [cm^{-1}] $\nu_{C\equiv N}$	$\nu_{C=O}$
3a	35	132–133°	133–134°[17]	2230	1680
3b	83	158–159°	159–160°[17]	2230	1650
3c	86	192–194°	$C_{14}H_9FN_2O$ (240.2)	2240	1660
3d	87	180–181°	$C_{14}H_9ClN_2O$ (256.7)	2235	1650
3e	80	216–218°	$C_{14}H_9N_3O_3$ (267.3)	2230	1670
3f	75	151–152°	$C_{12}H_8N_2OS$ (228.3)	2225	1640

[a] Yield of pure, isolated product.
[b] Recrystallised from chloroform/hexane.
[c] The microanalyses were in good agreement with the calculated values: C, ±0.25; H, ±0.20; N, ±0.20; Cl, ±0.10; S, ±0.15.
[d] Pye-Unicam SP 1100 Spectrometer.

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