Use of Substituted Acetamides for the Synthesis of 3-Substituted 2-Aminoquinolines

Mahendra D. Chordia, Sanjay N. Karmarkar, Shriniwas L. Kelkar, Murzban S. Wadia*

Department of Chemistry, University of Poona, Poona-411007, India

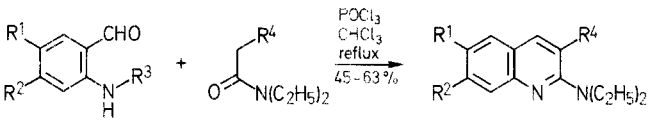
A novel two-step conversion of 2-aminobenzaldehydes to 3-substituted 2-diethylaminoquinolines utilizes a modified Friedländer reaction in which a substituted acetamide is used, for the first time, as a source of the C_2 unit.

Heteroannelation of 2-aminobenzaldehydes is a subject of current interest and has been recently reviewed.[1,2] The Friedländer synthesis and its modifications[1,2] is a method of wide synthetic utility for the conversion of 2-aminobenzaldehydes to quinolines. The present two-step conversion of 2-aminobenzaldehydes to hitherto unknown 3-substituted 2-diethylaminoquinolines represents a new modification which involves, for the first time, the use of *N,N*-diethylacetamides as a source of two additional carbon atoms. The advantages of this method reside in the predetermined direction of ring closure, the direct and regiospecific introduction of substituents into the newly formed heterocyclic ring, and the variety of substituents that can be incorporated into the starting compound. Another important feature of the present method is the production of a quinoline functionalized at the 2 position whereas the Friedländer method is more useful for the synthesis of quinolines functionalized at the 3 position.

Treatment of the aminoaldehyde **1a**[3] with the preformed complex of phosphoryl chloride and *N,N*-diethylphenylacetamide **(2a)** resulted in a vigorous reaction. Since attempts to control this reaction were unsuccessful, the aminoaldehydes was acetylated to give the acetanilide **1b** in 60% yield. The reaction of **1b** with the above preformed complex in chloroform afforded a syrupy liquid after work-up (Table). The absence of carbonyl, hydroxy, and amino absorptions in the IR spectrum ruled out the initially expected structure **4**. The ^{1}H-NMR signals assignable to -NEt_2 (0.98, t, 6 H; 3.2, q, 4 H), OCH_2O (6.0, s, 2 H), and aromatic protons (7.22–7.56, m, 5 H; 6.92, 7.18, 2 s, 1 H each, 8-H, 5-H; 7.60, 1 H, s, 4-H) coupled with the IR data and the mode of formation clearly required the compound to have structure **3ba**. The product was obtained in 63% yield.

Similar reactions of the acetanilide **1b** with other amides **2b–e** afforded products identified as the quinolines **3bb–be** by their mode of formation in combination with their spectral and analytical data. These products were obtained in yields varying from 44 to 60%, while the reactions of acetanilide **1c**[4] with the amides **2a** and **2b** furnished **3ca** and **3cb**, respectively.

The reactions of unsubstituted 2-aminoobenzaldehyde **(1d)** with amides **2** afforded different types of products. Their structures are under investigation.



1a-d **2a-e** **3ba-be ca-cb**

1	R^1	R^2	R^3
a	OCH_2O		H
b	OCH_2O		$COCH_3$
c	OCH_3	OCH_3	$COCH_3$
d	H	H	H

2	R^3
a	C_6H_5
b	Cl
c	CH_3
d	OC_6H_5
e	*O*-(2-naphthyl)

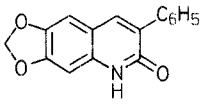


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Table. 3-Substituted 2-Diethylaminoquinolines **3** Prepared

Product	Time (h)	Yield[a] (%)	m.p. (°C)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS), δ[c]					
					$N(CH_2-CH_3)_2$ (t)	$N(CH_2-CH_3)_2$ (q)	OCH_2O or OCH_3 (s)	8-H, 5-H (s)	4-H (s)	Other H_{arom} (m)
3ba	24	63	syrupy liquid	$C_{20}H_{20}N_2O_2$ (320.4)	0.98	3.2	6.0	6.92, 7.18	7.60	7.22–7.56
3bb	24	48	70–72	$C_{14}H_{15}ClN_2O_2$ (278.7)	1.19	3.44	5.97	6.77, 7.03	7.70	–
3bc	24	53	syrupy liquid	$C_{15}H_{18}N_2O_2$ (258.3)	1.04	3.34	6.03	6.93, 7.24	7.64	[d]
3bd	18	60	108	$C_{20}H_{20}N_2O_3$ (336.4)	1.04	3.58	6.0	6.73, 7.09	7.22	6.88–7.38
3be	16	48	syrupy liquid	$C_{24}H_{22}N_2O_3$ (386.4)	1.17	3.53	5.93	6.72, 7.14	7.29	7.24–7.48
3ca	24	45	95–97	$C_{21}H_{24}N_2O_2$ (336.4)	1.10	3.29	3.90 3.97	6.82, 7.00	7.53	7.13–7.31
3cb	24	45	syrupy liquid	$C_{15}H_{19}ClN_2O_2$ (294.8)	1.27	3.49	3.94 4.02	6.79, 7.09	7.79	–

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.2.
[c] Recorded on a Perkin Elmer R-32, 90 MHz instrument.
[d] Additional 3H at δ = 2.34 (s) for Ar–CH_3.

3-Substituted 2-Diethylaminoquinolines (3); General Procedure:
Phosphoryl chloride (0.154 g, 1 mmol) is added at 0°C to a stirred solution of the acetamide **2a–e** (1 mmol) in dry $CHCl_3$ (10 mL). To this complex, the acetanilide **1b** or **1c** (1 mmol) is added. The mixture is heated to reflux for 18–24 h, then cooled. The $CHCl_3$ is removed and 10% Na_2CO_3 solution (10 mL) is added. This mixture is warmed on a water bath (60°C) for 10 min, then cooled, acidified with dilute HCl, and extracted with $CHCl_3$ (2 × 25 mL). The $CHCl_3$ extract is washed with water, dried (Na_2SO_4), concentrated, and passed through a short column of silica gel (10 g). Elution with hexane gives the pure product **3**.

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