The Preparation of Isoquinoline-*N*-imines by the Reaction of 1-Acyl-2-(2′-oxoalkyl)-arenes with Hydrazides

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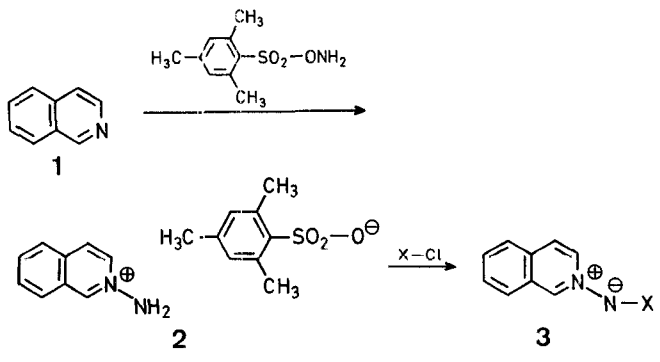
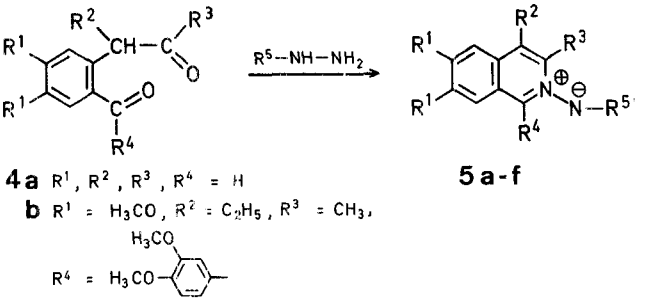
Several routes to isoquinoline *N*-acyl- and -sulphonyl-imines **3** are known[1,2,3]. The most commonly used is that involving amination of the parent heterocycle **1** using *O*-mesitylene sulphonylhydroxylamine followed by reaction of the resulting *N*-amino mesitylenesulphonate **2** with the required acylating reagent in the presence of a base[1]. Studies of the cycloaddition reactions of such compounds have been reported[4,5,6].



X = acyl or sulphonyl

We have found that compounds of this type can be most conveniently prepared by the reactions of 1-acyl-2-(2′-oxoalkyl)-arenes **4** with hydrazides. This reaction constructs the *N*-functionalised heterocyclic ring in one step. Two types of dicarbonyl compounds have been used: the dialdehyde **4a** which gave the unsubstituted isoquinoline derivatives **5a–d**, and the diketone **4b** which gave the highly substituted isoquinoline *N*-imines **5e, f**. It is notable that the latter, obtained in good yield by this method, could not be prepared via the amination/acylation sequence on the preformed isoquinoline[7].

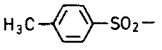
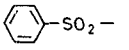
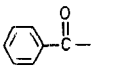
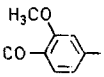
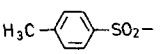
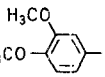
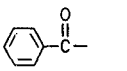


4a R^1, R^2, R^3, R^4 = H

b R^1 = H_3CO, R^2 = C_2H_5, R^3 = CH_3,

R^4 =

5a-f

5	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	
b	H	H	H	H	
c	H	H	H	H	H_3C-SO_2-
d	H	H	H	H	
e	H_3CO	C_2H_5	CH_3		
f	H_3CO	C_2H_5	CH_3		

This method provides particularly easy access to the unsubstituted systems **5a–d** as homophthalaldehyde **(4a)** can be readily prepared by the oxidative cleavage of indene[8,9,10]. Substituted dicarbonyl compounds are accessible by similar procedures[9,10]. The isoquinoline system itself has recently been prepared by the reaction of homophthalaldehyde and its substituted analogues with ammonia[9,10].

A simple experimental procedure was followed in the reactions using homophthalaldehyde **(4a)**. The reactants in solution in ethanol together with added hydrochloric acid as catalyst were stirred at room temperature for two days after which the product was filtered off. The ease of carrying out the reaction and the ready availability of the reactants compensates for the generally moderate yields (33–82%). Higher yields could probably be obtained by further work-up of the filtrates. The procedure followed in the reactions with the diketone **4b**, which involved pouring the reaction mixture into sodium carbonate solution followed by solvent extraction, gave better yields (63–85%).

The ^{1}H-N.M.R. spectra of compounds **5e** and **5f** showed evidence of restricted rotation – presumably about the $N^{\ominus}$-SO_2 and $N^{\ominus}$-CO bonds. In the *N*-sulphonylimine **5e** the effect on the spectrum at room temperature was small, shown only in the broadening of one of the CH_3O absorptions. However, in the spectrum of the *N*-benzoylimine **5f** only one of the CH_3O groups gave a single peak, the other three and the methyl group each gave rise to a pair of peaks in a ~60:40 ratio and the peaks due to the ethyl group were

broad. In a variable temperature study carried out in diphenyl ether it was observed that the peaks due to the CH_3O and CH_3 groups broadened with increasing temperature, coalesced at 90–110 °C and gave sharp singlets at 160 °C. The original spectrum was restored on cooling.

^{1}H-N.M.R. spectra were obtained on Varian HA100 and Bruker WP200 spectrometers. Chemical shifts are recorded as δ values.

Reaction of Homophthalaldehyde[8] (4a) with *p*-Toluenesulphonylhydrazide; Typical Procedure:

A mixture of the dialdehyde **4a** (0.23 g, 1.55 mmol), *p*-toluenesulphonylhydrazide (0.29 g, 1.55 mmol) and concentrated hydrochloric acid (4 drops) in ethanol (10 ml) is stirred at room temperature for two days. The white precipitate (0.247 g) is filtered off and recrystallised from ethanol to give *isoquinoline*-N-p-*toluenesulphonylimine* (**5a**); yield: 0.198 g (43%); m.p. 226–228 °C (Lit.[1], m.p. 228–229 °C). Repetition of the reaction gave yields of 52% and 47%.

Isoquinoline-N-*benzenesulphonylimine* (**5b**); prepared similarly from **4a** and benzenesulphonylhydrazide; yield: 37%; m.p. 258–260 °C (from ethanol) (Lit.[3], m.p. 258–260 °C).

Isoquinoline-N-*methanesulphonylimine hydrochloride* (**5c**); prepared similarly from **4a** and methanesulphonylhydrazide[11]; yield: 82%; m.p. 195 °C.

$C_{10}H_{11}N_2ClO_2S$	calc.	C 46.42	H 4.29	N 10.83
(258.7)	found	46.6	4.3	10.8

I.R. (Nujol); ν = 2450 (br., NH); 1360, 1155 cm^{-1} (SO_2).

^{1}H-N.M.R. (DMSO-d_6, 100 MHz): δ = 2.70 (s, 3H, CH_3), 7.8–8.6 (m, 6H$_{arom}$); 9.70 ppm (d, 1H, J = 1 Hz, H-1).

Isoquinoline-N-*benzoylimine* (**5d**); prepared similarly from **4a** and benzoylhydrazide[12], yield: 42%; m.p. 188–189 °C (from ethanol) (Lit.[1], m.p. 188 °C).

The products **5a**, **5b**, and **5d** had ^{1}H-N.M.R. and I.R. spectra identical with those reported[1].

Reaction of 2-(1-Ethylacetonyl)-3′,4,4′,5-tetramethoxybenzophenone[13] (4b) with *p*-Toluenesulphonylhydrazide:

A mixture of the diketone **4b** (0.268 g, 0.694 mmol), *p*-toluenesulphonylhydrazide (0.136 g, 0.732 mmol) and concentrated hydrochloric acid (6 drops) in ethanol (7 ml) is boiled under reflux in the dark for 20 min. After cooling the mixture is added with stirring to aqueous sodium carbonate solution (0.5 g in 125 ml water). This solution is then continuously extracted with benzene for 6 h. Evaporation of the benzene gives a yellow gum (0.441 g) which is crystallised from benzene/light petroleum (b.p. 60–80 °C) to give *4-ethyl-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-3-methylisoquinoline* N-p-*toluenesulphonylimine* (**5e**); yield: 0.316 g (85%); m.p. 206–207 °C.

$C_{29}H_{32}N_2O_6S$	calc.	C 64.91	H 6.01	N 5.22
(536.6)	found	65.15	6.05	5.1

^{1}H-N.M.R. ($CDCl_3$, 100 MHz): δ = 1.35 (t, 3H, J = 7 Hz, CH_2CH_3); 2.30 (s, 3H, H_3C—C_6H_4—); 2.99 (s, 3H, 3—CH_3); 3.13 (q, 2H, J = 7 Hz, CH_2CH_3); 3.66 (s, 3H, OCH_3); 3.74 (br. s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.07 (s, 3H, OCH_3); 6.45–7.3 ppm (m, 9H$_{arom}$).

Reaction of 4b with Benzoylhydrazide:

A mixture of the diketone **4b** (0.293 g, 0.758 mmol), benzoylhydrazide[12] (0.110 g, 0.808 mmol) and concentrated hydrochloric acid (6 drops) in ethanol (5 ml) is boiled under reflux for 20 min. Work-up as described for **5e** above and crystallisation from benzene/chloroform gives *4-ethyl-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-3-methylisoquinoline*-N-*benzoylimine* (**5f**); yield: 0.231 g (63%); m.p. 225–227 °C (dec.).

$C_{29}H_{30}N_2O_5$	calc.	C 71.59	H 6.22	N 5.76
(486.6)	found	71.5	6.2	5.5

I.R. (Nujol): ν = 1601 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$, 200 MHz, −23 °C): δ = 1.33 (br. t, 3H, J = 7 Hz, CH_2CH_3); 2.72, 2.74 (2s, ratio 40:60, 3—CH_3); 3.15 (br.q, 2H, J = 7 Hz, CH_2CH_3); 3.69, 3.74 (2s, ratio 60:40, OCH_3); 3.76, 3.85 (2s, ratio 60:40, OCH_3); 3.89, 3.91 (2s, ratio 40:60, OCH_3); 4.11 (s, 3H, OCH_3); 6.8–7.9 ppm (m, 10H$_{arom}$).

In diphenyl ether as solvent at 28 °C (using $CDCl_3$ autolock) the methoxy groups gave a similar set of absorptions at δ = 3.18 (s, 3H); 3.10, 2.99 (3H, ratio 40:60); 3.07, 2.90 (3H, ratio 60:40); 2.87, 2.84 ppm (3H, ratio 60:40); on heating the last three sets broadened, coalesced at 90–110 °C, and at 160 °C gave singlets at δ = 3.01, 2.98 and 2.86 ppm.

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[1] B. Agai, K. Lempert, *Tetrahedron* **28**, 2069 (1972).
[2] R.A. Abramovitch, T. Takaya, *J. Org. Chem.* **37**, 2022 (1972).
[3] P.N. Anderson, J.T. Sharp, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1331.
[4] R. Huisgen, R. Grashey, R. Krischke, *Tetrahedron Lett.* **1962**, 387.
[5] Y. Tamura, Y. Miki, M. Ikeda, *J. Heterocyclic Chem.* **12**, 119 (1975).
[6] R.J. Sundberg, J.E. Ellis, *J. Heterocyclic Chem.* **19**, 573 (1982).
[7] M. Lempert-Sréter, *Acta Chim. Acad. Sci. Hung.* **83**, 115 (1974).
[8] J.L. Warnell, R.L. Shriner, *J. Am. Chem. Soc.* **79**, 3165 (1957); see Refs.[9, 10] for more recent methods.
[9] R.B. Miller, J.M. Frincke, *J. Org. Chem.* **45**, 5312, (1980).
[10] R.B. Woodward, T.R. Hoye, *J. Am. Chem. Soc.* **99**, 8007 (1977).
[11] H. Kloes, *German Patent* 1069637 (1959); *C.A.* **56**, 327 (1962).
[12] T. Curtius, G. Struve, *J. Prakt. Chem.* **50**, 295 (1894).
[13] J. Korosi, G. Szabo, A. Lay, *Hung. Teljes* 488; *C.A.* **74**, 42168 (1971).