Synthesis of Hydrazone Derivatives by Reaction of Azines with Nitriles, and Their Transformation into Pyrazoles and Pyrimidones

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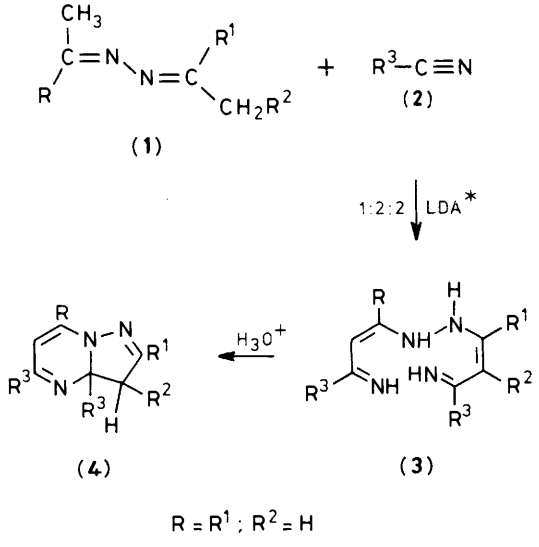
Reaction of equimolar amounts of saturated nitriles and azines affords hydrazone derivatives; with unsymmetrical azines the reaction is regioselective and takes place with an alkyl substituent at the end of the azines opposite to an aryl substituent. Acid catalysed cyclisation and hydrolysis of the hydrazone derivatives yields *N*-unsubstituted pyrazoles, whereas aluminium chloride catalysed cyclisation of the *N*-ethoxycarbonyl analogues affords pyrimidones.

1-Azabutadiene derivatives[1] are obtained by addition of the C_α–H of ketimines (ketene imines) to saturated nitriles and are versatile substrates for the synthesis of five-[2] and six-[3] membered heterocycles. Our continuing interest in new synthetic routes to heterocycles led us to study the reaction of azines with saturated nitriles in order to produce, by a simple route, starting materials suitable for the synthesis of more complex heterocycles.

Azines are excellent precursors for heterocycles mainly *via* cycloaddition reactions.[4] However, a few cases are known in which the heterocyclisation proceeds by reaction of the imine C_α–H.[5] Further, azines derived from acetophenone can be transformed into the corresponding dianions and alkylated by benzyl chloride.[6]

In a preliminary communication we have reported on the reactivity of the ketazine (ketone azine) C_α–H towards saturated nitriles. This reaction takes place with addition of two molecular equivalents of nitrile to the starting azine to yield hydrazine derivatives. The hydrazines (**3**) isolated are converted into 3*H*-pyrazolo[1,5-*a*]pyrimidines[7] by treatment with mineral acids (Scheme 1).



Scheme 1. * LDA = lithium di-isopropylamide

We have now thoroughly studied the reaction of both symmetrically and unsymmetrically substituted azines with saturated nitriles in order to obtain hydrazone derivatives (**5**) and explore their ability to give new heterocyclisation reactions. We have found that these new compounds (**5**) are suitable starting materials for the synthesis of pyrimidones by reaction with ethyl chloroformate.

When symmetrical azines (**1**) react with saturated nitriles and lithium di-isopropylamide (LDA) in a stoicheiometric ratio the hydrazonic derivatives (**5**) are obtained in high yield (see Table 1) although in some cases the formation of the corresponding hydrazine derivatives (**3**) was detected.

We have explored the possibility of performing regioselective monoadditions of azines to nitriles by using unsymmetrical substituted azines derived from aromatic hydrazones and aliphatic ketones[8] whose activated C_α–H groups at each side of the molecule exhibit significant differences in their reactivity.

In the reaction of (**1**; R = alkyl, R^1 = aryl) and (**2**) with LDA the addition occurs through the C_α–H group at the aliphatic side of the azine in a regioselective manner. Diaddition compounds are formed only when the process is carried out with an excess of nitrile and LDA. However, when $R^2 \neq H$ only compounds (**5**) are obtained irrespective of the molar ratio used. In these processes the enhanced reactivity of the imine C_α–H at the aliphatic side of the unsymmetrical azine in relation to the C_α–H bonded to the aryl group is clearly demonstrated.

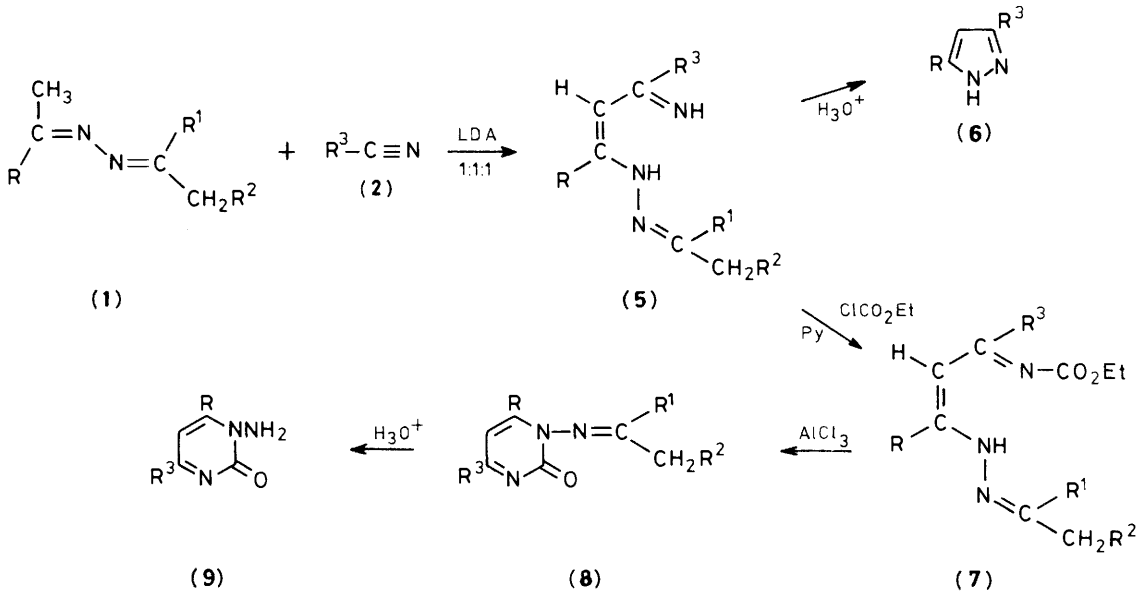
Compounds (**5**) were characterised on the basis of their elemental analyses and spectral data. All of them display in their i.r. spectra a clear absorption at *ca.* 3 400 cm^{-1} (NH). In the ^1H n.m.r. spectra the appearance of a singlet centred at *ca.* δ 5 p.p.m. which is assigned to the =CH grouping is typically present. The ^{13}C n.m.r. spectra show a single signal (doublet in off-resonance experiments), centred at 93—96 p.p.m., in the range of 80—110 p.p.m., suggesting an enamine group.[9]

The behaviour of compounds (**5**) towards acids was studied in order to learn about their reactivity and also to see whether this would provide a synthetic route to heterocycles.† *N*-Unsubstituted pyrazoles (**6**) were obtained when a solution of (**5**) in THF was treated with 2M-H_2SO_4 at room temperature. The structure of (**6**) was determined by means of an alternative synthesis from the corresponding 1,3-dicarbonyl compounds and hydrazine.[10] The formation of the pyrazoles (**6**) can be rationalised in terms of the nucleophilic attack of the sp^2 hybridised hydrazonic nitrogen on the imine C=N double bond.

Ethyl chloroformate reacts with 4-amino-1-azabutadienes to yield pyrimidine-2(1*H*)-ones in a regioselective manner.[11] For this reason, we also studied the behaviour of (**5**) towards ethyl chloroformate as a route to N-functionalised pyrimidones. However, more vigorous reaction conditions are required than in the cases in which the parent azabutadienes were used in a similar process.

When (**5**) reacts with ethyl chloroformate in pyridine as solvent, at room temperature, only mono-condensation products (**7**) are isolated. The latter show in their i.r. spectra characteristic absorptions at 3 300 (NH) and 1 780 (CO) cm^{-1}. The ^1H n.m.r.

† A study of the reactions of (**3**) and (**5**) with other systems is currently in progress.



Scheme 2.

Table 1. Hydrazonic derivatives (**5**) and pyrazoles (**6**)

Product	R	R^1	R^2	R^3	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N
(5a)	Me	Me	H	Ph	65	91—92	72.55 (72.52)	7.95 (7.96)	19.5 (19.52)
(5b)	Me	Me	H	*p*-Tolyl	70	114—115	73.3 (73.32)	8.35 (8.35)	18.35 (18.32)
(5c)	Ph	Ph	H	Cyclohexyl	60	142—143	79.95 (79.96)	7.85 (7.88)	12.15 (12.16)
(5d)	*p*-ClC_6H_4	*p*-ClC_6H_4	H	Cyclohexyl	63	170—172	66.65 (66.66)	6.05 (6.08)	10.1 (10.14)
(5e)	*p*-Tolyl	*p*-Tolyl	H	Cyclohexyl	65	177—178	80.4 (80.41)	8.35 (8.36)	11.25 (11.25)
(5f)	Me	Ph	H	Ph	64	124—126	77.9 (77.94)	6.9 (6.92)	15.1 (15.14)
(5g)	Me	Ph	H	*p*-Tolyl	70	152—153	78.3 (78.31)	7.3 (7.28)	14.4 (14.41)
(5h)	Me	Ph	H	*p*-ClC_6H_4	69	165—166	69.25 (69.37)	5.8 (5.83)	13.5 (13.47)
(5i)	Me	*p*-ClC_6H_4	H	*p*-Tolyl	70	195—196	70.05 (70.04)	6.2 (6.19)	12.9 (12.90)
(5j)	Me	Ph	Me	Ph	65	76—77	78.3 (78.32)	7.25 (7.26)	14.4 (14.42)
(5k)	Me	Ph	Me	*p*-Tolyl	75	126—127	78.65 (78.65)	7.6 (7.59)	13.75 (13.76)
(5l)	Me	Ph	Me	*p*-ClC_6H_4	70	143—144	70.05 (70.04)	6.15 (6.19)	12.9 (12.90)
(6a)	Me			Ph	73	126—127	75.9 (75.92)	6.35 (6.37)	17.7 (17.71)
(6b)	Me			*p*-Tolyl	76	122—123	76.7 (76.71)	7.05 (7.02)	16.25 (16.27)
(6c)	Ph			Cyclohexyl	77	141—143	79.6 (79.60)	8.05 (8.02)	12.35 (12.38)
(6d)	*p*-ClC_6H_4			Cyclohexyl	75	165—166	69.1 (69.09)	6.55 (6.57)	10.75 (10.74)
(6e)	*p*-Tolyl			Cyclohexyl	70	132—134	79.95 (79.95)	8.4 (8.39)	11.65 (11.66)
(6h)	Me			*p*-ClC_6H_4	77	147—148	76.45 (76.40)	5.75 (5.78)	17.8 (17.81)

spectrum displays a singlet at δ 5 p.p.m. corresponding to a =CH grouping. This carbon appears in the ^{13}C n.m.r. spectrum at δ 100 p.p.m. (doublet in off-resonance).

The cyclisation of (**7**) to afford the corresponding heterocycle (**8**) takes place under acid catalysis. Thus, a solution of compound (**7**) when treated with $AlCl_3$ at 60 °C, affords pyrimidones (**8**) in high yields (see Table 2). In addition, the 2M-H_2SO_4 hydrolysis of heterocycles (**8**) leads to *N*-amino-pyrimidones (**9**).

Compounds (**8**) and (**9**) were characterised on the basis of

Table 2. Compounds (7), (8), and (9)

Product	R	R^1	R^2	R^3	Yield (%)	M.p (°C)	Found (%) (Required) C	H	N
(7a)	Ph	Ph	H	Cyclohexyl	65	154—156	74.75 (74.79)	7.45 (7.48)	10.05 (10.06)
(7b)	*p*-ClC_6H_4	*p*-ClC_6H_4	H	Cyclohexyl	68	138—139	64.2 (64.20)	6.0 (6.01)	8.65 (8.64)
(7c)	*p*-Tolyl	*p*-Tolyl	H	Cyclohexyl	65	148—149	75.45 (75.47)	7.9 (7.92)	9.4 (9.43)
(7d)	Me	Ph	H	Ph	75	Oil	72.2 (72.18)	6.65 (6.63)	12.05 (12.03)
(7e)	Me	Ph	H	*p*-Tolyl	70	98—99	72.7 (72.70)	6.95 (6.93)	11.55 (11.56)
(7f)	Me	Ph	H	*p*-ClC_6H_4	68	122—123	72.4 (72.39)	6.35 (6.36)	12.05 (12.06)
(7g)	Me	Ph	Me	*p*-Tolyl	70	Oil	73.15 (73.18)	7.2 (7.21)	11.1 (11.13)
(7h)	Me	Ph	Me	*p*-ClC_6H_4	70	Oil	72.9 (72.90)	6.7 (6.67)	11.6 (11.59)
(8a)	Ph	Ph	H	Cyclohexyl	85	138—139	77.6 (77.60)	6.8 (6.78)	11.3 (11.31)
(8b)	*p*-ClC_6H_4	*p*-ClC_6H_4	H	Cyclohexyl	79	171—173	65.45 (65.46)	5.25 (5.26)	9.55 (9.54)
(8c)	*p*-Tolyl	*p*-Tolyl	H	Cyclohexyl	80	182—184	78.15 (78.16)	7.35 (7.32)	10.5 (10.52)
(8d)	Me	Ph	H	Ph	83	153—154	75.2 (75.23)	5.65 (5.65)	13.85 (13.85)
(8e)	Me	Ph	H	*p*-Tolyl	82	227—228	75.65 (75.69)	6.05 (6.03)	13.25 (13.24)
(8f)	Me	Ph	H	*p*-ClC_6H_4	82	167—168	75.45 (75.48)	5.35 (5.33)	13.9 (13.90)
(8g)	Me	Ph	Me	*p*-Tolyl	85	155—156	76.1 (76.11)	6.4 (6.39)	12.7 (12.68)
(8h)	Me	Ph	Me	*p*-ClC_6H_4	88	145—146	75.9 (75.93)	5.7 (5.73)	13.25 (13.28)
(9a)	Ph			Cyclohexyl	75	130—131	71.35 (71.35)	7.1 (7.11)	15.6 (15.60)
(9b)	*p*-ClC_6H_4			Cyclohexyl	77	145—147	63.25 (63.26)	5.95 (5.97)	13.8 (13.83)
(9d)	Me			Ph	78	257—258	65.65 (65.66)	5.5 (5.51)	20.85 (20.88)
(9e)	Me			*p*-Tolyl	75	208—209	66.95 (66.96)	6.1 (6.09)	19.55 (19.52)
(9f)	Me			*p*-ClC_6H_4	79	180—182	66.0 (65.99)	5.0 (5.03)	21.0 (20.99)

their elemental analyses and spectral data. Both classes of compounds show in their i.r. spectra absorption at 1 700 (CO) cm^{-1} and, in the case of (9), at 3 200 and 3 300 (NH_2) cm^{-1}. In the ^1H n.m.r. spectra of compounds (8) and (9) there was a singlet centred at *ca.* δ 6 p.p.m. corresponding to the =CH ring proton. This carbon appears in the ^{13}C n.m.r. spectrum at *ca.* δ 100 p.p.m.

Experimental

General.—Melting points were taken on samples in open capillary tubes in a Buchi melting-point apparatus and are uncorrected. The n.m.r. spectra were obtained using a Varian FT-80 n.m.r. spectrometer using deuteriated chloroform or deuteriated Me_2SO as solvent and shifts are reported in p.p.m. downfield (δ) from an internal $SiMe_4$ (TMS) standard. I.r. spectra were recorded in Nujol suspension on a Pye Unicam SP-1000 spectrophotometer. Microanalyses were performed on a Perkin-Elmer Model 240 instrument.

Supplementary Material.—Full ^1H n.m.r. and ^{13}C n.m.r. data for compounds (5) and (6) and full ^1H and ^{13}C n.m.r. data for compounds (7), (8), and (9) are available as a Supplementary publication [SUP. No. 23833 (6 pages)].*

Hydrazone Derivatives (5)*: General Procedure.*—*Acetone* 3-*imino*-1-*methyl*-3-*phenylprop*-1-*enylhydrazone* (**5a**). A solution of acetone azine (1.1 g, 10 mmol) in ether or THF was added to LDA (10 mmol) at 0 °C. After 20 min the mixture was cooled at −78 °C and benzonitrile (1.0 g, 10 mmol) added. The mixture was stirred at room temperature for 20 h after which it was poured into ice–water. The organic layer was extracted with ether and THF and the combined extracts dried (Na_2SO_4), filtered, and evaporated. The residue was purified by recrystallisation from hot hexane–chloroform to afford (**5a**) (1.4 g, 65%); $\nu_{max.}$ (Nujol) 3 350 and 1 600 cm^{-1}; δ_H ($CDCl_3$, internal $SiMe_4$) 2.0 (3 H, s, Me), 2.1 (3 H, s, Me), 2.2 (3 H, s, Me), 5.0 (1 H, s, =CH), 7.0—7.3 (1 H, m, NH), and 7.3—8.0 (5 H, m, ArH); δ_C ($CDCl_3$, internal $SiMe_4$) 165.2 (s), 160.1 (s), 152.9 (s), 139.4 (s), 129.4, 128.8, 126.2, 95.3 (d), 23.8 (q), 19.8 (q), and 18.7 (q); *m/z* 215 (M^+).

* For details of the Supplementary Publication scheme see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans 1*, 1984, Issue 1.

Pyrazoles (**6**): *General Procedure.*—*5-Methyl-3-phenylpyrazole* (**6a**). To a solution of (**5a**) (2.1 g, 10 mmol) in THF, 2M-H_2SO_4 (50 ml) was added and the solution stirred for 4 h at room temperature; it was then poured into ice–water and extracted with ether. The dry organic layer was evaporated and the residue recrystallised from hexane to afford (**6a**) (1.1 g, 73%); $\nu_{max.}$ (Nujol) 3 540 and 1 580 cm^{-1}; δ_H ($CDCl_3$, internal $SiMe_4$) 2.1 (3 H, s, Me), 6.1 (1 H, s, =CH), 7.0—7.8 (5 H, m, ArH), and 11.1 (1 H, m, NH); δ_C ($CDCl_3$, internal $SiMe_4$) 149.7 (s), 143.1 (s), 132.5 (s), 128.5, 127.6, 125.7, 101.9 (d), and 11.4 (q).

Products (**7**): *General Procedure.*—*Ethyl 3-(α-methylbenzylidenehydrazino)-1-(p-tolyl)but-2-enylideneaminoformate* (**7e**). Ethyl chloroformate (4.8 ml, 50 mmol) was added to a solution of (**5g**) (2.9 g, 10 mmol) in pyridine (100 ml); the solution was cooled at 0 °C during the addition. After being stirred at room temperature for 12 h the mixture was poured into ice cooled 1M-H_2SO_4 and extracted with ether. The dry organic layer was evaporated and the residue recrystallised from hot hexane–chloroform to afford (**7e**) (2.5 g, 70%); $\nu_{max.}$ (Nujol) 3 300 and 1 780 cm^{-1}; δ_H ($CDCl_3$, internal $SiMe_4$) 1.2 (3 H, t, Me), 2.2 (3 H, s, Me), 2.3 (3 H, s, Me), 2.4 (3 H, s, Me), 4.1 (2 H, q, CH_2), 5.3 (1 H, s, =CH), 7.0—8.1 (9 H, m, ArH), 11.0—11.3 (1 H, m, NH); δ_C ($CDCl_3$, internal $SiMe_4$) 164.7 (s), 160.3 (s) 153.4 (s), 146.8 (s), 138.7 (s), 138.5 (s), 134.0 (s), 129.8, 128.9, 128.1, 127.6, 126.7, 108.0 (d), 60.9 (t), 21.1 (q), 19.6 (q), 14.9 (q), and 14.1 (q); *m/z* 363 (M^+).

N-*Iminopyrimidones* (**8**): *General Procedure.*—*6-Methyl-1-(α-methylbenzylideneimino)-4-(p-tolyl)pyrimidin-2(1H)-one* (**8e**). To a solution of (**7e**) (3.6 g, 10 mmol) in dry THF, $AlCl_3$ (2.0 g, 15 mmol) was added with cooling during the addition. The mixture was heated for 15 h under reflux after which it was cooled, hydrolysed with ice–water, and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), evaporated, and the residue crystallized from hexane–chloroform to afford (**8e**) (2.6 g, 82%); $\nu_{max.}$ (Nujol) 1 680 cm^{-1}; δ_H ($CDCl_3$, internal $SiMe_4$) 2.2 (3 H, s, Me), 2.3 (3 H, s, Me), 2.4 (3 H, s, Me), 6.7 (1 H, s, =CH), and 7.0—8.1 (9 H, m, ArH); δ_C ($CDCl_3$, internal $SiMe_4$) 175.2 (s), 167.6 (s), 152.2 (s), 151.7 (s), 135.4 (s), 133.0 (s), 131.4 (s), 129.0, 128.4, 128.1, 127.4, 127.2, 100.3 (d), 21.1 (q), 19.0 (q), and 16.6 (q); *m/z* 317 (M^+).

N-*Aminopyrimidones* (**9**): *General Procedure.*—*1-Amino-6-methyl-4-phenylpyrimidin-2(1H)-one* (**9e**). A solution of (**8e**) (3.2 g, 10 mmol) in THF (50 ml) was treated with 2M-H_2SO_4 (50 ml) at room temperature during 10 h. The resulting solution was extracted with ether, dried, and evaporated to give (**9e**) (1.6 g, 75%) after recrystallisation in ethanol; $\nu_{max.}$ (Nujol) 3 320, 3 250, and 1 650 cm^{-1}; δ_H [$(CD_3)_2SO$, external $SiMe_4$] 2.1 (3 H, s, Me), 2.2 (3 H, s, Me), 5.9 (2 H, s, NH_2), 6.7 (1 H, s, =CH), and 6.8—7.8 (4 H, m, ArH); δ_C [$(CD_3)_2SO$, external $SiMe_4$] 164.5 (s), 157.0 (s), 155.0 (s), 141.2 (s), 133.5 (s), 129.3, 127.2, 100.6 (d), 20.9 (q), and 18.9 (q); *m/z* 215 (M^+).

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Received 8*th July* 1983; *Paper* 3/1169