A New Approach for the Synthesis of Fused Imidazoles: The Synthesis of 3-Acyl-Substituted Imidazo[1,2-*x*]azines

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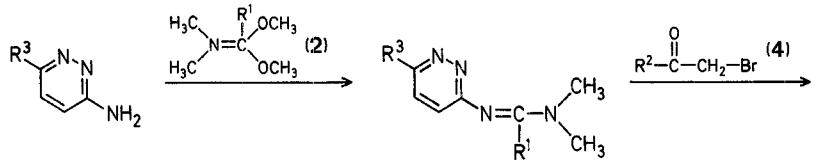
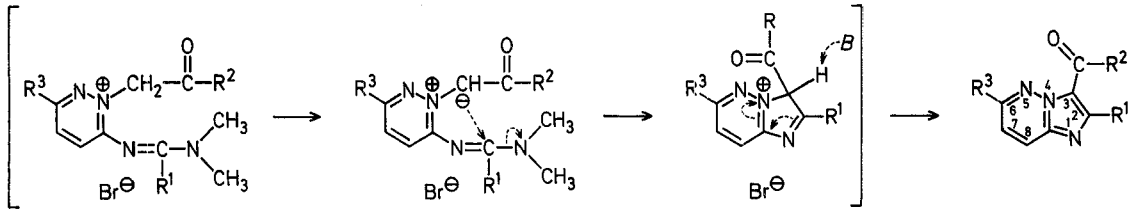
The most common methods for the synthesis of fused imidazo-azoles and imidazo-azines are the condensation of heterocyclic amines with α-halocarbonyl or related compounds, such as acetals of α-haloaldehydes[1], α-ketoaldehydes in acidic media[2,3], and formaldehyde and sodium cyanide[2]. Other methods involve the reaction of chloroazines with α-aminoacetaldehyde diethyl acetal[4,5], the displacement of the methylthio group with ethanolamine followed by cyclization and oxidation[4], and the treatment of α-amino-heterocyclic compounds with 1,2-dibromoethane followed by oxidation[6]. A common feature of all these methods is that C-2 and C-3 of the newly formed imidazole ring, together with the corresponding substituents, are contributed by the reagent used for cyclization. Thus, with haloacetaldehyde at position 2 and 3 unsubstituted imidazo[1,2-*x*]azines can be prepared. α-Haloketones or esters of β-halo-α-keto acids give the corresponding 2-substituted imidazo[1,2-*x*]azines, while with esters of α-halo-β-keto acids the corresponding 2,3-disubstituted imidazo[1,2-*x*]azines are obtained.

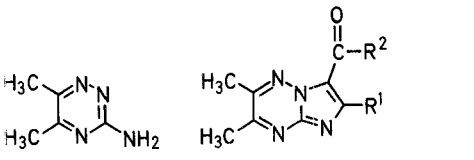


1 3

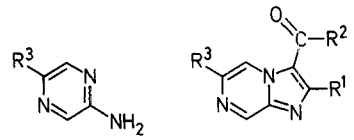


5 a-d

5	R^1	R^2	R^3	R^4
a	H	CH_3	Cl	H
b	H	C_6H_5	Cl	H
c	CH_3	CH_3	Cl	H
d	CH_3	C_6H_5	Cl	H

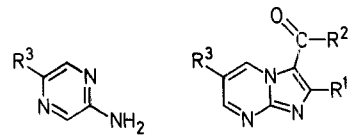


6 **5e** $R^1=CH_3, R^2=C_6H_5, R^3=CH_3$

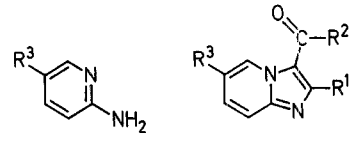


7 **5f** $R^1=H$, $R^2=C_6H_5$, $R^3=H$

5g $R^1=CH_3$, $R^2=C_6H_5$, $R^3=H$



8 **5h** $R^1=H$, $R^2=C_6H_5$, $R^3=H$



9 **5i** $R^1=CH_3$, $R^2=C_6H_5$, $R^3=H$

Recently, *N*-heteroarylformamidines and *N*-heteroarylformamide oximes have been found to be versatile intermediates for the preparation of various fused heterocyclic systems, such as azolo- and azinoimidazoles, triazoles, oxazoles, pyrimidines, furans, etc.[7].

As an extension of this type of reactions, we report a new synthesis of imidazo[1,2-*x*]azines, in which the C-2—C-3 bond of the imidazole ring is formed.

Treatment of the *N,N*-dimethyl-*N'*-heteroaryl-formamidines (**3**; $R^1=H$) and *N,N*-dimethyl-*N'*-heteroarylacetamidines (**3**; $R^1=CH_3$), obtained from the corresponding heterocyclic amines **1**, **6**, **7**, **8**, or **9** and *N,N*-dimethylformamide dimethyl acetal (**2**; $R^1=H$) or *N,N*-dimethylacetamide dimethyl acetal (**2**; $R^1=CH_3$), respectively[8-11], with α-bromoketones **4**, such as bromoacetone or phenacyl bromide, affords 3-substituted or 2,3-disubstituted imidazo[1,2-*x*]azines **5**. The reaction proceeds most probably first as a quaternization at the ring nitrogen, analogously to the previously reported quaternization with methyl iodide[8]. Intramolecular nucleophilic attack of the anion of the quaternary group to the carbon atom of the amidine group, followed by elimination of dimethylamine or protonated dimethylamine, affords the fused imidazo[1,2-*x*]azine systems **5**.

Contrary to the previously described methods, in which C-2 and C-3, together with the corresponding substituents, are contributed by the reagent used for cyclization, in this synthesis C-2 and the R^1 group is introduced by the acetal used for the preparation of the amidine, while C-3 and the CO—R^2 group is dependent on the α-bromoketone **4** used for cyclization. Reaction proceeds under mild conditions in neutral solvents, such as methanol, ethanol, or dimethylformamide, dependent on the solubility of the amidines. In some instances, the hydrobromide salts of the final products could be isolated, since hydrogen bromide is formed during the reaction.

In this manner, derivatives of 3-acetyl- or 3-benzoyl-substituted imidazo[1,2-*b*]pyridazine **5a**, **5b**, **5c**, and **5d**, imidazo[1,2-*a*]pyridine **5i**, imidazo[1,2-*a*]pyrimidine **5h**, imidazo[1,2-*a*]pyrazine **5f** and **5g**, and imidazo[1,2-*b*][1,2,4]triazine **5e** were prepared.

The method represents a new general synthesis of 3-substituted and 2,3-disubstituted imidazo[1,2-*x*]azines. This is also the only approach for the synthesis of 3-acyl-substituted derivatives of these systems, a class of compounds which has not been reported before.

The following compounds **3** were prepared in essentially the same way as reported in literature: *N,N*-dimethyl-*N'*-(6-chloropyridazin-3-yl)-formamidine[8], *N,N*-dimethyl-*N'*-(6-chloropyridazin-3-yl)-acetamidine[9], *N,N*-dimethyl-*N'*-(pyrazin-2-yl)-formamidine[10], *N,N*-dimethyl-*N'*-(pyrimidin-2-yl)-formamidine[10], *N,N*-dimethyl-*N'*-(pyrid-2-yl)-acetamidine[9], *N,N*-dimethyl-*N'*-(pyrazin-2-yl)-acetamidine[9], and *N,N*-dimethyl-*N'*-(5,6-dimethyl-1,2,4-triazin-3-yl)-acetamidine[11].

Table. 3-Acyl- and 3-Acyl-2-methyl-imidazo[1,2-*x*]azines **5** prepared

Product	Reaction Conditions solvent/time/temp.	Yield [%][a]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. *m/e* (rel. int. %)	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
5a	C_2H_5OH/24 h/r.t.	50[c]	131–132° (*c*-C_6H_{12})	$C_8H_6ClN_3O$ (195.6)	195 (M^+, 52)	2.70 (s, 3 H, CO—CH_3); 7.14 (d, 1 H, 7-H); 7.92 (d, 1 H, 8-H); 8.28 (s, 1 H, 2-H); $J_{7\text{-H},8\text{-H}}$ = 9.0 Hz
5b	DMF/1 h/reflux	42	259–260° (CH_3OH)	$C_{13}H_8ClN_3O$ (257.7)	257 (M^+, 100)	7.30 (d, 1 H, 7-H); 7.4–7.7 + 7.8–8.05 (2 m, 5 H_{arom}); 8.05 (d, 1 H, 8-H); 8.15 (s, 1 H, 2-H); $J_{7\text{-H},8\text{-H}}$ = 9.0 Hz
5c	C_2H_5OH/24 h/r.t.	45[c]	164–165° (*c*-C_6H_{12})	$C_9H_8ClN_3O$ (209.6)	209 (M^+, 100)	2.70 (s, 3 H, 2-CH_3); 2.78 (s, 3 H, CO—CH_3); 7.10 (d, 1 H, 7-H); 7.80 (d, 1 H, 8-H); $J_{7\text{-H},8\text{-H}}$ = 9.2 Hz
5d	*c*-C_6H_{12}/2 h/reflux	55	127–129° (*c*-C_6H_{12})	$C_{14}H_{10}ClN_3O$ (271.7)	271 (M^+, 100)	2.44 (s, 3 H, 2-CH_3); 7.05 (d, 1 H, 7-H); 7.25–7.8 (m, 5 H_{arom}); 7.80 (d, 1 H, H-8); $J_{7\text{-H},8\text{-H}}$ = 9.0 Hz
5e	DMF/2 h/reflux	60	223–224° (*c*-C_6H_{12}/$CHCl_3$)	$C_{15}H_{14}N_4O$ (266.3)	266 (M^+, 85)	2.42 (s, 3 H, 2-CH_3); 2.50 and 2.62 (2 s, 3 H each, 6-CH_3, 7-CH_3); 7.3–7.9 (m, 5 H_{arom})
5f	C_2H_5OH/1 h/reflux	23	194–195° (CH_3OH)	$C_{13}H_9N_3O$ (223.2)	223 (M^+, 100)	7.45–7.70 and 7.8–8.05 (2 m, 5 H_{arom}); 8.24 (d, 1 H, 6-H); 8.30 (s, 1 H, 2-H); 9.20 (d, 1 H, 8-H); 9.53 (dd, 1 H, 5-H); $J_{5\text{-H},8\text{-H}}$ = 1.5 Hz; $J_{5\text{-H},6\text{-H}}$ = 4.8 Hz
5g	CH_3OH/1 h/reflux	17	152° (*c*-C_6H_{12}/$CHCl_3$)	$C_{14}H_{11}N_3O$ (237.3)	237 (M^+, 100)	2.25 (s, 3 H, 2-CH_3); 7.18 (d, 1 H, 6-H); 7.45–7.9 (m, 5 H_{arom}); 9.20 (s, 1 H, 8-H); 9.25 (d, 1 H, 5-H); $J_{5\text{-H},6\text{-H}}$ = 5.0 Hz
5h	CH_3OH/2 h/reflux	68	234–235° ($CHCl_3$/CH_3OH)	$C_{13}H_9N_3O$ (223.2)	223 (M^+, 100)	7.13 (dd, 1 H, 6-H); 7.4–7.65 and 7.75–7.95 (2 m, 5 H_{arom}); 8.35 (s, 1 H, 2-H); 8.75 (dd, 1 H, 7-H); 9.93 (dd, 1 H, 5 H); $J_{5\text{-H},6\text{-H}}$ = 6.8 Hz; $J_{6\text{-H},7\text{-H}}$ = 3.6 Hz; $J_{5\text{-H},7\text{-H}}$ = 2.1 Hz
5i · HBr	C_2H_5OH/2 h/reflux	16	250–251° (*c*-C_6H_{12}/$CHCl_3$)	$C_{15}H_{13}BrN_2O$ (317.2)	236 (M^+ − HBr, 100)	2.20 (s, 3 H, 2-CH_3); 7.4–7.6 (m, 5 H_{arom}, 6-H, 7-H); 8.0 (m, 1 H, 8-H); 9.3 (m, 1 H, 5-H)[d]

[a] Yield of pure, isolated product, not optimized.
[b] Satisfactory microanalyses obtained: C ±0.44, H ±0.13, N ±0.37.
[c] For isolation, see experimental section.
[d] In DMSO-d_6.

3-Acyl- and 3-Acyl-2-methylimidazo[1,2-*x*]azines (5); General Procedure:

To a solution of *N,N*-dimethyl-*N'*-heteroarylformamidine **3** (R^1 = H; 2 mmol) or *N,N*-dimethyl-*N'*-heteroarylacetamidine **3** (R^1 = CH_3, 2 mmol) in an appropriate solvent (3 to 5 ml) the α-bromoketone **4** (2.25 mmol) is added and the mixture heated at reflux temperature for 1–2 h unless otherwise stated. The solvent is evaporated in vacuo. A few milliliters of the solvent used for recrystallization are added to the residue which is left in refrigerator overnight. The crystalline product **5** is separated by filtration and recrystallized from an appropriate solvent (Table).

Isolation of 5a and 5c:

The residue obtained by evaporation of solvent in vacuo is dissolved in water (5 ml) and methanol (2 ml), neutralized by addition of solid sodium hydrogen carbonate and extracted with chloroform (3 × 10 ml). The combined extracts are dried with anhydrous sodium sulphate, and the residue obtained after evaporation of chloroform in vacuo is purified by sublimation (160°C/2 torr) to give **5a** and **5c**, respectively. For further details see the Table.

Received: August 22, 1983

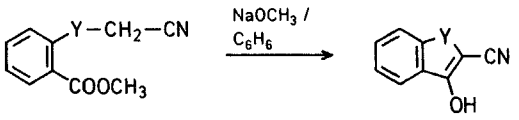
[1] For a review see: J. P. Paolini, in: *Special Topics in Heterocyclic Chemistry*, A. Weissberger, E. C. Taylor, Eds., John Wiley & Sons, New York, 1977, pp. 1–115.
[2] G. Maury, in: *Special Topics in Heterocyclic Chemistry*, A. Weissberger, E. C. Taylor, Eds., John Wiley & Sons, New York, 1977, pp. 179–244.
[3] G. B. Barlin, I. L. Brown, L. Golič, V. Kaučič, *Aust. J. Chem.* **35**, 423 (1982).
[4] W. L. F. Armarego, *J. Chem. Soc.* **1965**, 2778.
[5] B. Stanovnik, M. Tišler, M. Ceglar, V. Bah, *J. Org. Chem.* **35**, 1138 (1970).
[6] For a review see: M. Tišler, B. Stanovnik, in: *Condensed Pyridazines Including Cinnolines and Phthalazines*, R. N. Castle, Ed., John Wiley & Sons, New York, 1973, pp. 761–1056.
[7] For a review on the recently developed syntheses in this area see: B. Stanovnik, *Chem. Zvesti (Chemical Papers)* **36**, 693 (1982); *C. A.* **98**, 71962 (1983).
[8] M. Zupan, V. Pirc, A. Pollak, B. Stanovnik, M. Tišler, *J. Heterocyclic Chem.* **11**, 525 (1974).
[9] M. Drobnič-Košorok, S. Polanc, B. Stanovnik, M. Tišler, B. Verček, *J. Heterocyclic Chem.* **15**, 1105 (1978).
[10] S. Polanc, B. Verček, B. Šek, B. Stanovnik, M. Tišler, *J. Org. Chem.* **39**, 2143 (1974).
[11] B. Stanovnik, A. Štimac, M. Tišler, B. Verček, *J. Heterocyclic Chem.* **19**, 577 (1982).

Errata and Addenda 1984

M.H. Elnagdi, M.R.H. Elmoghayar, G.E.H. Elgemeie, *Synthesis* **1984** (1), 1–26:

The second paragraph on page 2 should read:
Cyclic 3-oxoalkanenitriles **11** are obtained via cyclisation of methyl *N*-acetyl-*N*-cyanomethylanthranilate (**10a**)[61a], methyl 2-(cyanomethoxy)-benzoate (**10b**)[61b], or methyl 2-(cyanomethylthio)-benzoate (**10c**)[61] under basic conditions.

The formula scheme **10** → **11** (p. 3) should be:



10a Y = N–CO–CH$_3$ **b** Y = O **c** Y = S

11a-c

The experimental procedure for **11a** (p. 3) should read:

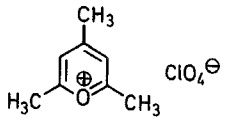
2-Cyano-3-hydroxyindole (11a; Y = NH)[61]:
A mixture of freshly prepared sodium methoxide (10 mmol) and methyl *N*-acetyl-*N*-cyanomethylanthranilate (**10a**; 10 mmol) in benzene (25 ml) is stirred for 2 h at room temperature then left for 12 h at room temperature. The mixture is poured into water. Carbon dioxide is bubbled into the resulting solution till no more solid separates. The product is collected and recrystallised; yield: 64%; m.p. 165–167°C (dec.).

The following references should be added (p. 23):

[61] (a) D. Vorländer, *Ber. Dtsch. Chem. Ges.* **35**, 1683, 1696 (1902).
(b) R. Bryant, D.L. Haslam, *J. Chem. Soc.* **1965**, 2361.

P. Molina, A. Tárraga, E. Romero, M.L. Peña, *Synthesis* **1984** (1), 71–73:

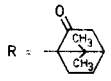
The structure of compound **6** (p. 71) should be:



6

Abstract 6803, *Synthesis* **1984** (1), 82:

The substituent R should be:

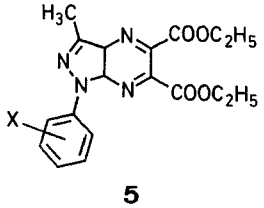


F. Pochat, *Synthesis* **1984** (2), 146–148:

Compounds **3c**, **5c**, and **5g** (p. 147 and 148) should be named as *N'*-acyl-*N'*-(methylthiomethyl)-hydrazones.

P.G. Baraldi, D. Simoni, V. Periotto, S. Manfredini, M. Guarneri, *Synthesis* **1984** (2), 148–149:

The structure of compound **5** (p. 149) should be:



5

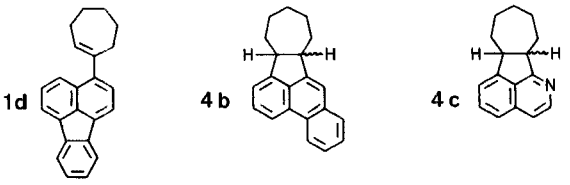
S.C.W. Coltman, S.C. Eyley, R.A. Raphael, *Synthesis* **1984** (2), 150–152:

The first line of the experimental procedure for esters **4** should read:
To a solution of **2** (0.1 mol) in absolute ethanol (30 ml) is added a l

R. Lapouyade, A. Nourmamode, *Synthesis* **1984** (2), 161–164:

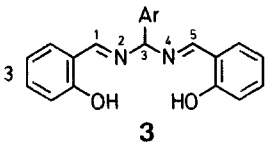
The title should read:
A New Synthesis of 6b,8,9,10,11,11a-Hexahydro-7*H*-cyclohepta[*a*]acenaphthylenes by Base-Catalyzed Photocyclization of 1-Arylcycloheptenes

The structures of products **1d**, **4b**, and **4c** in Tables 2 and 3 (p. 163) should be:



T. Takajo, S. Kambe, W. Ando, *Synthesis* **1984** (3), 256–259:

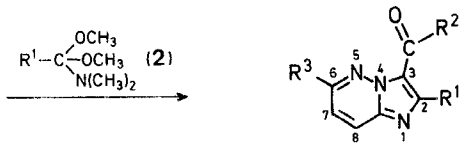
The structure of product **3** (p. 257, left) should be:



3

S. Podergajs, B. Stanovnik, M. Tišler, *Synthesis* **1984** (3), 263–265:

The structures of reagent **2** and products **5a–d** (p. 264) should be:



5a-d

U. Schöllkopf, U. Busse, R. Kilger, P. Lehr, *Synthesis* **1984** (3), 271–274:

The heading for the first experimental procedure (p. 274) should be:
(3*S*,6*S*)-3,6-Diisobutyl-2,5-dioxohexahydropyrazine (**9**):

J. Cabré, A.L. Palomo, *Synthesis* **1984** (5), 413–417:

The authors' address should read:
Gema S.A., Beethoven-15, Barcelona-21; Centro Marga para la Investigación, Muntaner 212, Barcelona-36, Spain
The formulae of Schemes **A** and **B** (p. 413) should be interchanged.
The following experimental procedure should be added:

Cyclohexylammonium Carboxylates (Tables 3); General Procedure:
To a solution of cyclohexylamine (1.15 ml, 10.0 mmol) in the solvent (20 ml, Table 3), the carboxylic acid is added at room temperature. The mixture is stirred for 15 min at room temperature and then cooled to 0–5°C. The precipitate is filtered and washed with cold (0 to −5°C) solvent (10 ml).

D.P. Stack, R.M. Coates, *Synthesis* **1984** (5), 434–436:

The structure of product **2e** (Table, p. 435) should be: