Syntheses of 2-Arylimidazole Derivatives through Annelations Employing Benzylamines

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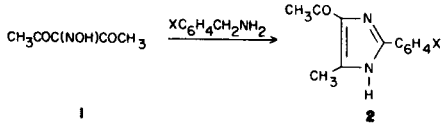
Annelations of benzylamines with hydroximino derivatives of pentane-2,4-dione or of alkyl acetoacetates, acetoacetamides, and acetoacetanilides, afford imidazole derivatives and provide easy incorporation of the benzylic carbon and nitrogen in the heterocycle. The limits of the reaction have been explored.

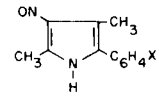
J. Heterocyclic Chem., **17**, 1723 (1980).

Annelation of 3-oximinopentane-2,4-dione **1** with benzylamine affords 4-acetyl-5-methyl-2-phenylimidazole **2a** (X = H) (1). To check the scope and limitations of this



1 **2**

reaction, we allowed benzylamines carrying different substituents on the phenyl group in the para position, to react with **1** and similar multifunctional compounds. Imidazole derivatives were obtained in all cases investigated (Table 1). No alternative pathways, as the one that would lead to a nitrosopyrrole (**3**), were uncovered.



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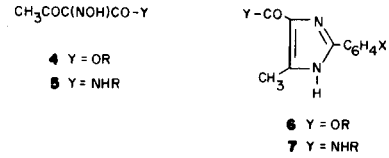
Analogous reactions of 2-oximinoacetoacetates (**4**) and 2-oximinoacetoacetamides (**5**) afforded the pertinent 4-carbalkoxy- and 4-carboxamido-5-methyl-2-phenylimidazoles (**6**, **7**).

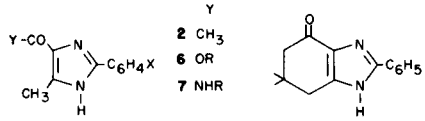


4 Y = OR
5 Y = NHR

6 Y = OR
7 Y = NHR

Table 1

Imidazole and Tetrahydrobenzimidazole Derivatives



2 CH$_3$
6 OR
7 NHR

10

Compounds No.	Y	X	Reagents $H_2NCH_2C_6H_4X$ and	Procedure Solvent (a)	Temperature	Time	Yields %	M.p., °C (Solvent) (a)	Formula	Analyses (Calcd./Found) C	H	N	Cl
2a	CH_3	H	**1**	A	reflux	2 hours	68	200-201 (A)	$C_{12}H_{12}N_2O$				
				D	20°	28 days	86						
				D	100°	3 hours (b)	74						
2b	CH_3	CH_3	**1**	A	reflux	2 hours	60	204-205 (T)	$C_{13}H_{14}N_2O$	72.87	6.59	13.08	
										72.74	6.58	13.19	
2c	CH_3	OCH_3	**1**	A	reflux	4 hours	56	162-164 (T)	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	
										67.75	6.22	11.99	
2d	CH_3	Cl	**1**	A	reflux	2.5 hours	66	224-226 (A)	$C_{12}H_{11}ClN_2O$	61.41	4.72	11.92	15.11
										61.26	4.75	11.94	15.15
2e	CH_3	NO_2	**1**	A	reflux	2 hours	72	299-300 (E)	$C_{12}H_{11}N_3O_3$	58.77	4.52	17.14	
										58.68	4.67	17.38	
6a	OCH_3	H	**4a**	A	reflux	3 hours	32	187-188 (T)	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.96	
										66.53	5.59	12.87	
6b	OC_2H_5	H	**4b**	A	reflux	3 hours	31	200-202 (e)	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	
										67.35	6.38	12.31	
7a	NHC_6H_4Clp	H	**5a**	A	20°	30 days	53	264-265 (T)	$C_{17}H_{13}Cl_2N_3O$	58.98	3.78	12.14	20.48
				D	20°	30 days	29			58.18	3.70	12.52	20.90
				– (c)	170°	13 minutes	27						
7b	NHC_6H_4Clp	NO_2	**5a** (d)	A	20°	3 days	31	295-296 (E)	$C_{17}H_{13}ClN_4O_3$	57.23	3.67	15.70	9.94
										57.05	3.77	15.45	10.05
7c	$NHCH_2C_6H_5$	NO_2	**5b** (d)	A	reflux	4 hours	52	227-229 (T)	$C_{18}H_{16}N_4O_3$	64.27	4.80	16.66	
										63.82	4.97	16.59	
10	—		**9**	See Experimental			83	250-251 (T)	$C_{12}H_{16}N_2O$	74.97	6.71	11.66	
										74.58	6.55	11.57	

(a) A: acetonitrile; D: dimethylsulfoxide; T: toluene; E: ethanol. (b) In this run, a sample of a condensation product from **1** and benzylamine was used. (c) In this run, a sample of a condensation product from **5a** and *p*-chlorobenzylamine was used. (d) In the presence of one equivalent of triethylamine. (e) Lit. (5) m.p. 199-199.5°.

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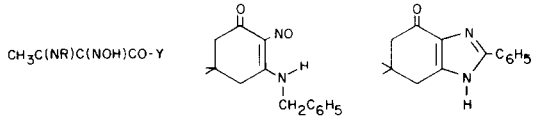
Table 2

Spectroscopic Parameters of the Derivatives of Table 1

Compound No.	Uv nm	(Ethanol) ε	Ir (Potassium Bromide), cm^{-1}. NH (a)	CO	Pmr (DMSO-d_6), δ CH_3 (singlets)	Ring NH (a)	Aromatic Protons
2a	287	29600	3250 (b)	1640	2.50, 2.54	13.0	7.47 (m, 3H), 8.02 (m, 2H)
2b	287	20200	3250	1640	2.47, 2.52	12.8	7.3, 7.9 (A_2B_2, J = 8 Hz)
2c	289	19650	3220	1640	2.48, 2.52	13.0	7.05, 7.95 (A_2B_2, J = 9 Hz)
2d	291	23250			2.48, 2.52	13.0	7.55, 8.0 (A_2B_2, J = 8 Hz)
2e	280	7200 (c)	3200	1650	2.50, 2.56	13.2	8.16, 8.3 (A_2B_2, J = 8 Hz)
6a	278	22600	3200	1700	2.52	12.9	7.5 (m, 3H), 8.0 (m, 2H)
6b	277	22700	3300	1710	2.56	12.6	7.4 (m, 3H), 8.0 (m, 2H)
7a	293	29670 (d)	3170	1660	2.62	12.8	7.3-8.2 ($2A_2B_2$) (d')
7b	275	27400 (e)	3380	1650	2.60	13.0	7.4, 7.9 (A_2B_2, J = 9 Hz)
7c	260	sh (f)					8.28, 8.34 (A_2B_2, J = 9 Hz) (e')
10	298	23500 (g)	3200	1650		13.2	7.5 (m, 2H), 8.1 (m, 2H)

(a) The ir and pmr signals for the NH groups are broad. (b) In chloroform, signals for free NH are at 3440 cm^{-1}. (c) λ max 229 (12370), 345 (20800). (d) 225 (sh), 275 (27580). (d') δ 9.8 (ArNH). (e) 351 (23000). (e') δ 9.85 (ArNH). (f) 232 (18000); 352 (16950). (g) 218 (15.200).

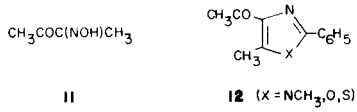
Under suitable conditions, compounds **2** and **7** arise also from the condensation products of **1** or **5** with benzylamines; such intermediates have been reported as Schiff bases (**8**), but their exact structures require further investigation (2). The bicyclic derivative **10** has been obtained, in turn, by ring closure of the nitrosoenaminone **9** (2c).



8 **9** **10**

The ring closure **9** → **10** is similar to the cyclodehydration of 4-amino-5-nitrosouracils to yield xanthines (3). Parallel investigations on the above mentioned reaction intermediates may contribute to understanding the cyclization mechanism. The possibility that tautomers of **8**, having a nitrosoenaminone structure analogous to **9**, are the actual intermediates, is worthy of consideration.

The hydroxyimino ketone **11** could not be converted into imidazole derivatives upon reaction with benzylamines under a variety of conditions. This points to the importance of an extra carbonyl group on the intermediate undergoing the cyclization.



11 **12** (X = NCH_3, O, S)

On the other hand, *N*-methylbenzylamine, benzyl alcohol and benzyl mercaptan proved unsuitable to give heterocyclic derivatives (**12**) in reactions with 3-oximinopentanedione (**1**), in several conditions.

EXPERIMENTAL

Melting points were determined in open capillary tubes or on a Reissert-Kofler hot plate and are uncorrected. Ultraviolet and infrared spectra were measured with 124DB and 157G Perkin Elmer spectrometers. ^{1}H-nmr spectra were taken on a Perkin Elmer R32 instrument, at 90 MHz, with tetramethylsilane as an internal standard. Chemical shifts are in parts per million (δ). Concentrations are 10% in the solvents indicated; NH signals were always broad.

Starting Materials.

3-Oximinopentanedione (**1**) was prepared by nitrosation of acetylacetone with amyl nitrite (C. Erba, Milano, Italy). Methyl and ethyl 2-oximinoacetoacetates (**4a,b**) were prepared according to the literature (4). *p*-Chloroacetacetanilide and *N*-benzylacetacetamide were purchased from K and K, ICN Pharmaceuticals, Inc., Plainview, N.Y. Nitrosation with sodium nitrite in acetic acid yielded 2-oximino-*p*-chloroacetacetanilide (**5a**), m.p. 176-177° (90%).

Anal. Calcd. for $C_{10}H_9ClN_2O_3$: C, 49.91; H, 3.76; N, 11.64. Cl, 14.73. Found: C, 49.88; H, 3.76; N, 11.75; Cl, 14.57.

2-Oximino-*N*-benzylacetacetamide (**5b**) was prepared in an analogous manner, m.p. 132-133° (82%).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.98; H, 5.49; N, 12.72. Found: C, 59.86; H, 5.67; N, 13.04.

Benzylamine, 4-methyl-, 4-methoxy-, 4-chloro-benzylamine were purchased from Fluka A.G. 4-Nitrobenzylamine hydrochloride was purchased from Ega-Chemie, Steinheim, W. Germany. The base was set free with 1*N* sodium hydroxide, extracted with chloroform and dried with sodium sulphate, and alternatively, with triethylamine, directly in the reaction vessel.

Examples of Reactions of 3-Oximinoacetylacetone **1**, 2-Oximinoacetoacetates **4**, or 2-Oximinoacetacetamides **5**, with Benzylamines.

General Procedure.

A 0.5 molar solution of **1**, **4** or **5** (0.005 mole) in 10 ml. of a solvent was treated with the appropriate benzylamine (0.0055 mole) and heated at reflux or allowed to stand, as indicated in Table 1. The products were obtained upon cooling and/or concentration; recrystallization solvents, yields of purified products, physical and analytical data are in Tables 1 and 2, unless otherwise specified.

DMSO was evaporated *in vacuo* and the crude product was purified using columns of silica or Sephadex, with chloroform as the eluant.

In the reactions without any solvent, the sample was dry-heated a few degrees higher than its melting point.

2-Phenyl-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzimidazole (**10**).

A sample of 2-nitroso-3-benzylamino-5,5-dimethyl cyclohexen-2-one (**9**) (2c) (0.4 g., 1.6 mmoles) in 10 ml. of toluene was heated at reflux for 15 minutes. The solid obtained was recrystallized from toluene (83%).

Reactions of **1** with *N*-Methylbenzylamine.

Samples of the reagents were allowed to react: 1) in acetonitrile at reflux up to 8 hours, eventually in the presence of one equivalent of triethylamine or acetic acid; and ii) in DMSO, at 20° up to 2 weeks. A reaction mixture of **1** (0.65 g., 0.005 mole) and *N*-methyl benzylamine (0.66 g., 0.0055 mole) in acetonitrile (13 ml.), was refluxed for 6 hours, followed by concentration and chromatography on a column of silica gel with ethyl acetate-toluene (1:1) as the eluant. *N*-benzylacetamide (identical to an authentic sample) was obtained (0.72 g., 88%). The same product was obtained under other conditions, in lower yields, together with unidentified by-products.

Reactions of **1** with Benzyl Alcohol and Benzyl Mercaptan.

Equimolecular amounts of **1** and either reagent were allowed to react in acetonitrile, chloroform, acetic acid or DMSO, alone or in the presence of triethylamine or acetic acid or acetic anhydride, at reflux for up to 3.5 hours, or at room temperature for up to 28 days. Benzyl mercaptan was also used without any solvent (molar ratio 1:40). Only the reagents were present under mild conditions; unidentified decomposition products formed under more drastic ones.

Acknowledgment.

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