ONE STAGE SYNTHESIS OF 5-DICYANOMETHYLENE-3,5-DIHYDRO-2H-BENZIMIDAZOLES

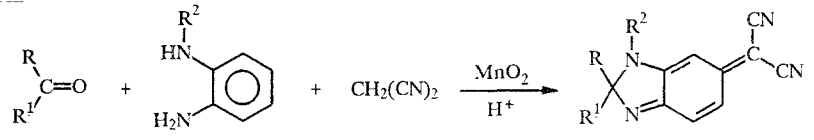
V. A. Kaminskii, O. G. Pestova, and L. V. Mezhennaya

Oxidative condensation of ketones, o-phenylenediamines, and malononitrile in the presence of acid catalysts and MnO_2 gives 5-dicyanomethylene-2-R-2-R'-3,5-dihydro-2H-benzimidazoles. Changing the mono ketones to 1,5-diketones leads to 8-dicyanomethylene-3,4,4a,8-tetrahydropyrido[1,2-a]benzimidazoles.

Several examples of the synthesis of 3,5-dihydro-2H-benzimidazoles as a class of methylene quinonimines. In one case the authors started from benzofurazan-N-oxides [1] and in a second the route involves condensation of o-phenylenediamine with ketones, oxidation of the benzimidazolines to 2H-benzimidazoles (isobenzimidazoles), and reaction with activated methylene compounds [2]. Similar derivatives can be obtained directly from benzimidazolines via oxidative condensation with malononitrile in the presence of MnO_2 [3]. In both of these methods the scope for ketone variation is limited because only cyclohexanone [2], substituted derivatives [4], and hetero analogs [3] form stable benzimidazolines. Attempts to use other ketones, in particular cyclopentanone and acyclic ketones, were unsuccessful [2].

We have found 5-dicyanomethylene-2-R-2-R'-3,5-dihydro-2H-benzimidazoles (Ia-g) can be synthesized in one step by a ternary oxidative condensation of ketones with o-phenylenediamine (OPD) and malononitrile in the presence of acid catalysts and MnO_2. In the absence of catalyst the main reaction is the oxidation of OPD. The catalysts include acetic and oxalic acids, HCl, and p-toluenesulfonic acid. In a number of examples better results were obtained using BF_3 etherate. The reactions occur at room temperature. With this method a wider range of ketones can be used (aliphatic including pinacolone, cyclopentanone) but the yields of the products are significantly lower than for cyclohexanone. Acetophenone does not form 3,5-dihydrobenzimidazoles under these conditions. Similar condensation of acetone with malononitrile and an N-substituted o-phenylenediamine N-(α-phenacylbenzyl)-o-phenylenediamine gave Ih.

Scheme 1



Ia-h

Ia–g R^2 = H a R = R^1 = CH_3; b R = CH_3, R^1 = C_2H_5; c R = CH_3, R^1 = C_4H_9; d R = CH_3, R^1 = *i*-C_4H_9; e R = CH_3, R^1 = *t*-C_4H_9; f R + R^1 = $(CH_2)_3$; g R + R^1 = $(CH_2)_4$; h R = R^1 = CH_3, R^2 = $C_6H_5COCH_2CHC_6H_5$

The same condensation can be carried out using 1,5-diketones IIa, b. The majority readily form stable condensation products with OPD which easily take part in an oxidative coupling reaction, in particular with maloninitrile [3]. However, for IIa, b the condensation products with OPD could not be obtained [5]. A one stage condensation of these ketones with OPD and malononitrile allowed us to obtain condensed 3,5-dihydro-2H-benzimidazoles (8-dicyanomethylene-3,4,4a,8-tetrahydropyrido[1,2-

Far Eastern State University, Vladivostok. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1494-1497, November, 1992. Original article submitted January 16, 1992.

0009-3122/92/2811-1277$12.50

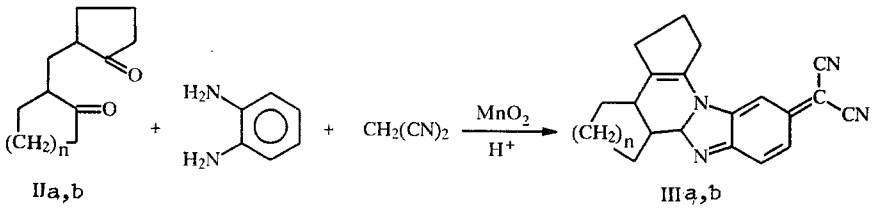
TABLE 1. PMR Spectra for 5-Dicyanomethylene-3,5-dihydro-2H-benzimidazoles (Ia, b, d-f, g)

Compound	Chemical shift, δ, ppm (spin–spin coupling, Hz)				
	4-H, d	6-H, dd	7-H, d (J = 10)	NH, br.s	other protons
Ia	6,18 (J=1,5)	7,39 (J=10; J=1,5)	7,10	7,19	1,62 s (6H, CH_3)
Ib	6,18 s	7,38 d (J=10)	7,12	7,74	0,83 t (3H, CH_3), 1,58 s (3H, CH_3), 2,00 q (2H, CH_2)
Id	6,17 (J=2)	7,38 (J=10; J=2)	7,12	7,94	0,90 t (6H, CH_3), 1,57 s (3H, CH_3), 1,35 m (CH), 1,84 d.d (J =-14; J = 6) (CH_2)
Ie	6,17 (J=2)	7,38 (J=10; J=2)	7,12	8,18	1,02 s (9H, CH_3), 1,54 s (3H, CH_3)
If	6,15 (J=2)	7,38 (J=10; J=2)	7,12	7,68	1,75 m (4H, CH_2), 2,06 m (4H, CH_2)
Ig	5,87 (J=2)	*	7,07	—	1,62 s (3H, CH_3), 1,68 s (3H, CH_3), 3,70 d.d (1H, J=-18; J=4,5), 4,12 d.d (1H, J=-18; J=7,5) (CH_2COPh), 5,90 (1H, J=7,5; J=4,5, CH)

*Masked by aromatic proton signals.

a]benzimidazoles IIIa, b) which are similar to those obtained earlier [3] from 1,5-diketones. The diketone IIb reacts more readily than IIa.

Scheme 2



IIa,b IIIa,b

II, IIIa n = 1; b n = 2

The IR spectra of all of the compounds prepared showed CN group absorption as a sharp band at 2200-2220 cm^{-1} and two strong quinonoid bands at 1620-1645 cm^{-1} and 1560-1590 cm^{-1}. The spectra of Ia-g also show absorption for NH at 3300 cm^{-1} and for Ih CO group absorption at 1686 cm^{-1}. With the exception of small differences in the "fingerprint" region the spectra of IIIa, b are extremely similar to those of the products previously obtained from alicyclic 1,5-diketones (2,2-methylenedicyclohexanone [3]). The structure of IIIb, in which a 6-membered and not 5-membered ring is spiro combined with imidazole, is assigned by analogy with the reaction product of IIb with o-aminophenol [5] since such a structure is less strained than the alternative (Table 1).

The PMR spectra of Ia-h (Table 1) show signals for the quinonoid protons 4-H, 6-H, and 7-H. Their appearance unambiguously points to the presence of a mono-substituted p-quinonoid structure. The signals for the other protons also agree with the proposed structures.

The mass spectrum of Ih shows a significant molecular ion (m/z 418) for the calculated molecular weight. Intense fragment peaks were also seen at m/z 209 (loss of the phenacylbenzyl fragment from the nitrogen atom) and at m/z 208 and 210 (fragmentation with fission of the chalcone).

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument using chloroform and PMR spectra on a Bruker WM-250 (250 MHz) using $CDCl_3$ solvent and TMS internal standard. Mass spectra were taken on an LKB 9000 with ionization intensity 70 eV and direct introduction of the sample. The course of the reaction and the product purities were monitored by TLC on Silufol plates.

Elemental analytical data for C, H, and N agreed with that calculated.

2,2-Dimethyl-5-dicyanomethylene-3,5-dihydro-2H-benzimidazole (Ia). OPD (1.0, 9 mmoles) and malononitrile (0.7 g, 11 mmoles) were dissolved in acetone (15 ml) and 10% oxalic acid solution (1 ml) in acetone was added with stirring (ODA oxalate precipitated). Activated MnO_2 (5 g, 55 mmoles) was added and the product was stirred for 1.5 h, filtered, and washed repeatedly with acetone. Acetone was removed from the combined filtrate and the residue was chromatographed on a silica gel column (100/250 micron) eluting with hexane–ethyl acetate (1:1) to give product (45%) with mp 239-241°C (literature data [1] 246°C). IR and PMR spectra agreed with the literature [1].

2-Methyl-2-ethyl-5-dicyanomethylene-3,5-dihydro-2H-benzimidazole (Ib, $C_{13}H_{12}N_4$). ODA (0.5 g, 4.5 mmoles) and malononitrile (0.5 g, 7 mmoles) were dissolved in methylethyl ketone (10 ml) and conc. HCl (3 drops) added. MnO_2 (2 g, 23 mmoles) was added with stirring and the stirring continued for 0.5 h, the MnO_2 filtered off, repeatedly washed with chloroform, and further treated as above to give Ib (44%) with mp 192-194°C.

5-Dicyanomethylene-2-R-2-R′-3,5-dihydro-2H-benzimidazoles (Ia-g). ODA (0.5, 4.5 mmoles) was dissolved in ethyl acetate (10 ml) and the ketone (1 ml, 2 ml for cyclopentanone) and a 10% solution of BF_3 etherate in ethyl acetate added. After 1-2 h, malononitrile (0.5-0.7 g) and MnO_2 (2.5 g) were added and the product stirred for 1-2 h. The product was worked up as for Ib to give Ic ($C_{15}H_{16}N_4$, 34%) with mp 194-196°C; Id ($C_{15}H_{16}N_4$, 22%) with mp 180-183°C; Ie ($C_{15}H_{16}N_4$, 19%) with mp 170-172°C; and If ($C_{14}H_{12}N_4$, 15%) with mp above 230°C (decomp.). Compounds Ig was obtained in 95% yield and was identical to a known sample by IR spectroscopy [3].

2,2-Dimethyl-5-dicyanomethylene-3-(α-phenyacylbenzyl)-3,5-dihydro-2H-benzimidazole (Ih, $C_{17}H_{22}N_4O$). N-(α-Phenacylbenzyl)-o-phenylenediamine (1 g, 3.2 mmoles) and malononitrile (0.3 g, 5 mmoles) were dissolved in acetone (30 ml) and acetic acid (3 drops) and MnO_2 (3 g, 32 mmoles) added. The product was stirred for 1 h and treated as for Ia to give Ih (30%) with mp 160-163°C.

1,2,4,4a-Bistrimethylene-8-dicyanomethylene-3,4,4a,8-tetrahydropyrido[1,2-a]benzimidazole (IIIa, $C_{20}H_{18}N_4$) and 1,2-Trimethylene-4,4a-tetramethylene-8-dicyano methylene-3,4,4a,8-tetrahydropyrido[1,2-a]benzimidazole (IIIb, $C_{21}H_{20}N_4$). A. ODA (1 g, 9 mmoles) and diketone IIa or IIb (4 g, ≃20 mmoles) were dissolved in chloroform (20 ml) and p-toluenesulfonic acid (50 mg) added. After 2 h malononitrile (1 g, 15 mmoles) in chloroform (10 ml) and MnO_2 (2.5 g, 23 mmoles) were added and stirred for 2 h, the MnO_2 filtered off, and washed with chloroform. The combined filtrates were evaporated to remove chloroform and the residue chromatographed on type II grade Al_2O_3 eluting IIIa with hexane–chloroform (2:1) or IIIb and hexane–chloroform (1:1). IIIa was obtained (14%) with mp 208-209°C and IIIb (47%) with mp 189-190°C.

B. A mixture of ODA (1 g), diketone IIa (1.7 g) and p-toluenesulfonic acid (50 mg) in xylene (30 ml) was refluxed for 3.5 h, the xylene evaporated under reduced pressure and the residue treated with chloroform (30 ml), and malononitrile (1.3 g). When the latter had dissolved, MnO_2 (2.5 g) was added and the product stirred for 1 h and worked up as in method A to give IIIa (41%).

All of the synthesized compounds were recrystallized from a mixture of benzene–hexane giving Ia-h as red crystals and IIIa, b as blue crystals. The yields were calculated based on ODA.

REFERENCES

1. D. W. S. Latham, O. Meth-Cohn, H. Suschitzky, and J. A. L. Herbert, J. Chem. Soc., Perkin I, No. 5, 470 (1977).
2. K. E. Davies, G. E. Domany, M. Farhat, J. A. L. Herbert, A. M. Jefferson, M. A. Gutierres, and H. Suschitzky, J. Chem. Soc., Perkin I, No. 11, 2465 (1984).
3. O. Yu. Slabko, L. V. Mezhennaya, V. A. Kaminskii, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 6, 779 (1990).
4. J. A. L. Herbert, B. Iddon, A. Robinson, and H. Suschitzky, J. Chem. Soc., Perkin I, No. 5, 991 (1988).
5. V. A. Kaminskii, I. V. Stepanchenko, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 9, 1251 (1979).
6. W. Ried and P. Stahlhofen, Chem. Ber., **90**, 815 (1957).