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IMIDAZOLE DERIVATIVES CONTAINING POTENTIALLY LABILE GROUPS ON THE $N_{(1)}$ ATOM

8*. SYNTHESIS OF N-AMINOIMIDAZOLES VIA 1-AMINO-3-METHOXYMETHYLIMIDAZOLIUM AND 1-AMINO-3-ACETYLIMIDAZOLIUM SALTS

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When O-picrylhydroxylamine is reacted with 1-methoxymethyl and 1-acetyl derivatives of imidazole, benzimidazole, 2-cyanomethylbenzimidazole, and perimidine, 1-amino-3-R-imidazolium, -benzimidazolium, and -perimidinium picrates are formed (R = CH_3OCH_2, CH_3CO). Their subsequent hydrolysis (spontaneous in the case of the N-acetyl derivatives) results in the elimination of the labile R substituent and the formation of the corresponding N-amino-imidazole or -perimidine. In a number of cases this is a more convenient method for their synthesis than the direct amination of NH-heterocycles in alkaline medium.

It has been established that the most convenient method for the preparation of N-aminoazoles is the electrophilic amination of NH-azoles with hydroxylamine O-sulfonic acid (HSA) in aqueous alkaline medium [2]. However, this method has a number of limitations, mainly relating to the ease of formation and reactivity of the azole N-anions via which the reaction proceeds. It cannot be easily applied to azoles having low NH-acidity (for example, imidazole) [3], or those yielding N-anions with low nucleophilicity (nitroazoles) [4] or low stability (perimidine) [5]. Considerable problem can also occur in the amination of compounds that contain in addition to the pyrrole NH group other acidic functional groups that form reactive anions. A number of ways of overcoming these problems have been proposed. Thus, for azoles with low NH-acidity or those forming anions with low nucleophilicity, the use of nonaqueous solvents and of bases stronger than sodium hydroxide is recommended [3, 6]. However, in this case there is a problem in the choice of aminating agent. Since HSA cannot be used in nonaqueous solvents, it is necessary to use more expensive and inaccessible reagents such as O-mesitylsulfonylhydroxylamine (MSH) [6], diphenylphosphinylhydroxylamine [3], or O-picrylhydroxylamine (PHA) [7]. An alternative method involves the amination of neutral azole bases followed by deprotonation of the resulting N-aminoazolium cation using potassium carbonate or sodium hydroxide. This method also requires the use of MSH or PHA as the aminating agent [7]. Furthermore, it has the disadvantage that the initial azole is itself capable of deprotonating the N-aminoazolium salt, which prevents it from reacting further and hence substantially reduces the yield of required product. It is worth noting that, in contrast to NH-azoles, N-substituted azoles when treated with MSH or PHA generally form N-aminoazolium salts in high yield [8, 9]. In this study we decided to cause azoles containing potentially labile N-substituents to undergo similar reactions. We considered that the latter could be readily removed after amination, which would be a further method of synthesizing N-aminoazoles that are difficult to obtain via N-anions. We selected methoxymethyl and acetyl groups as these labile groups. Studies were conducted on imidazole, benzimidazole, and perimidine compounds. Although benzimidazole is effectively aminated by HSA via the N-anion [10], it was taken as a convenient model compound.

*For Communication 7 see [1].

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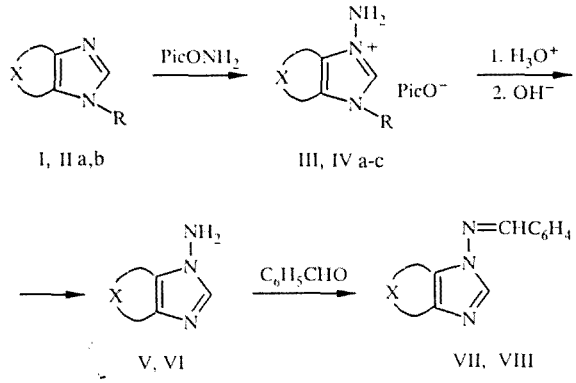


I, II a,b

III, IV a-c

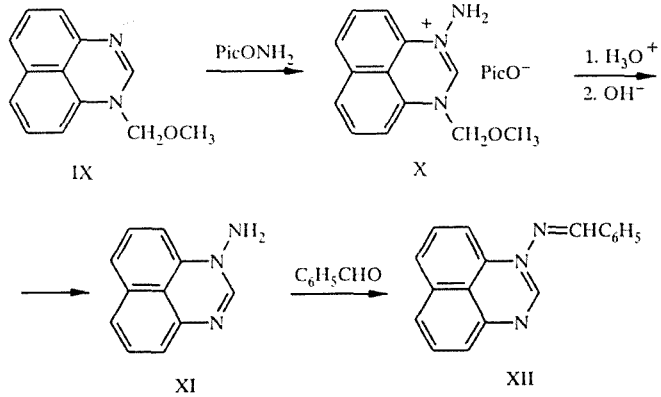
V, VI

VII, VIII

I, III, V, VII X = $(CH)_4$; II, IV, VI, VIII X = 2H; I—III a R = CH_2OCH_3, b R = $COCH_3$, c R = H;
Pic — picryl

As expected, on reaction with PHA in chloroform, compounds Ia and IIa form 1-amino-3-methoxymethylimidazolium salts IIIa and IVa in good yield. Their subsequent hydrolysis in concentrated hydrochloric acid occurs quite slowly and requires boiling over a period of hours. The yield of amines V and VI was 48 and 41% respectively, while the latter was only isolated as its benzylidene derivative VIII (it is not convenient to isolate this oily and very unstable amine as the free base). The immediate reaction product of the 1-acetyl derivatives Ib and IIb with PHS was the picrate of the corresponding amine (IIIc and IVc) in 72 and 84% yield respectively. The instability of salts such as IIIb and IVb which contain an energy-rich N-acyl bond is well-known [11]. In this case, in addition to the usual hydrolysis of this bond by traces of moisture that are present in the reaction mixture, the possibility of transfer of the acetyl group to the picryl anion can also assist in its decomposition. In fact, a certain quantity of picryl acetate is present in the filtrate that remains after separation of salts IIIc and IVc. Picrates IIIc and IVc can be converted in the usual manner to bases V and VI or to hydrazones VII and VIII.

Unfortunately, this approach did not prove to be very suitable for the synthesis of 1-aminoperimidine (XI). 1-Acetylperimidine is a compound that is not very stable and hence difficult to obtain [12]. As for methoxymethylperimidine (IX), it forms salt X in high yield when reacted with PHA. However, its subsequent acid hydrolysis is accompanied by tar formation, with the result that the yield of amine, which is isolated solely as the hydrazone XII, is not more than 5%. We attribute this to the well established high reactivity of the naphthalene ring in perimidines towards electrophilic reagents [13]. It is probable that the formaldehyde eliminated by hydrolytic cleavage of the methoxymethyl group reacts with perimidines to give polycondensation products such as phenol–formaldehyde resins.



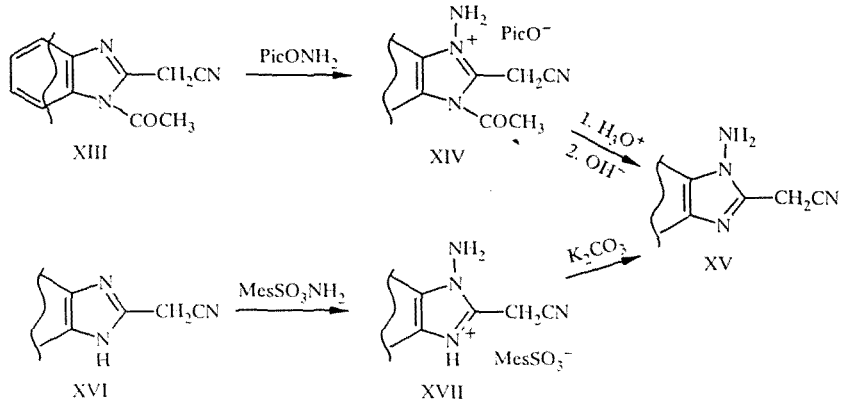
IX

X

XI

XII

As an example of a compound with several acidic sites, we chose 2-cyanomethylbenzimidazole (XVI), which has similar NH- and CH-acidity values $pK_a(NH)$ = 11.48 and $pK_a(CH)$ = 13.23 (in 50% aqueous acetone) [13]. Its 1-acetyl derivative XIII when treated with PHA was converted via salt XIV to the previously unknown 1-amino-2-cyanomethylbenzimidazole (XV), the yield of which was 17%. This method is better than the amination of compound XVI with HSA in alkaline medium, since in the latter case it is difficult to isolate amine XV from the large number of byproducts that are present in the reaction mixture. However, it still undergoes amination under neutral conditions with MSH, which makes it possible to obtain amine XV in 31% yield after treatment of the intermediate salt XVII with potassium carbonate.



It may be concluded from this study that it is possible in principle to use N-protected groups for the preparation of N-aminoazoles via N-aminoazolium salts. Of greater future potential is the use of an N-acetyl group for this purpose, which would merit further research studies.

EXPERIMENTAL

The PMR spectra were recorded on a Unity-300 instrument with working frequency 300 MHz and TMS as the internal standard. The IR spectra were obtained in vaseline oil on an IKS-40 instrument. The course of the reactions and the purity of the compounds obtained were monitored by TLC on plates with Al_2O_3 of grade IV activity. The melting points were measured in sealed glass capillaries on a PTP instrument and were uncorrected.

The carbon and hydrogen elemental analysis data for compounds IIIa,b, IVa,b, X, and XV corresponded to the calculated values.

1-Amino-3-methoxymethylbenzimidazolium Picrate (IIIa, $C_{15}H_{14}N_6O_8$). To a solution of 0.31 g (1.9 mmole) of 1-methoxymethylbenzimidazole in 3 ml of chloroform was added a solution of 0.6 g (2.46 mmole) of PHA in 18 ml of chloroform. The mixture was agitated for 1 h at 55-60°C and the precipitate of salt IIIa was filtered off. Yield 0.56 g (72%); golden-yellow crystals with mp 120-123°C (ethanol). IR spectrum: 3380, 3110 (NH_2), 1635 cm^{-1} (C=N). PMR spectrum (DMSO-d_6): 3.35 (s, 3H, CH_3), 5.85 (s, 2H, CH_2), 7.0 (br. s, 2H, NH_2), 7.69-7.8 (m, 2H, 5-H, 6-H), 7.95-8.1 (m, 2H, 4-H, 7-H), 8.59 (s, 2H, 3′-H, 5′-H), 9.98 ppm (s, 1H, 2-H).

1-Amino-3-methoxymethylimidazolium Picrate (IVa, $C_{11}H_{12}N_6O_8$). This was obtained in a similar manner to salt IIIa from 0.28 g (2.5 mmole) of 1-methyoxymethylimidazole and 1.22 g (5 mmole) of PHA. Yield 0.7 g (79%); orange-brown needles with mp 97-101°C (ethanol). IR spectrum: 3307, 3139 (NH_2), 1612 cm^{-1} (C=N). PMR spectrum (DMSO-d_6): 3.3 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 6.3-7.4 (br. s, 2H, NH_2), 7.71 (t, 1H, 4-H), 7.81 (t, 1H, 5-H), 8.6 (s, 2H, 3′-H, 5′-H), 9.34 ppm (t, 1H, 2-H); $J_{2\text{-}4} = J_{2\text{-}5} = J_{4\text{-}5} = 1.9$ Hz.

Hydrolysis of Salt IIIa. Salt IIIa (0.25 g; 0.63 mmole) was refluxed with 5 ml of conc. HCl for 8.5 h. After cooling, the mixture was neutralized with conc. ammonia to pH 7, the picric acid was extracted with chloroform (3 × 15 ml), and the 1-aminobenzimidazole was extracted with ethyl acetate (3 × 20 ml). The ethyl acetate extract was concentrated down to 1/3 of its volume and passed through an Al_2O_3 column (l = 25 cm, d = 2 cm) with chloroform as eluant. 1-Aminobenzimidazole was eluted as a colorless fraction with R_f 0.24. Yield 47 mg (56%); mp 155-156°C (in agreement with the literature [10]).

Hydrolysis of Salt IVa. A solution of 0.2 g (0.56 mmole) of salt IVa in 5 ml of conc. HCl was refluxed for 30 h, after which it was evaporated to dryness; 3 ml of acetic acid and 0.1 ml (1 mmole) of benzaldehyde were added and the mixture was refluxed for 40 min. The mixture was concentrated down to 1/3 of its original volume and the residue was diluted with 1 ml of water, neutralized with ammonia to pH 7, and evaporated to dryness under vacuum. The dry residue was extracted with 10 ml of chloroform and the extract was passed through an Al_2O_3 column (l = 25 cm, d = 2 cm) with chloroform as eluant. 1-Benzylidenaminoimidazole (VIII) was eluted as a colorless fraction with R_f 0.49. Yield 45 mg (47%); colorless needless with mp 115-116°C (in agreement with the literature [3]), PMR spectrum ($CDCl_3$); 7.17 (s, 1H, 4-H), 7.43-7.55 (m, 4H, 5-H, 3′-H to 5′-H), 7.82 (m, 2H, 2′-H, 6′-H), 7.98 (s, 1H, 2-H), 8.48 ppm (s, 1H, N=CH).

1-Aminobenzimidazolium Picrate (IIIc, $C_{13}H_{10}N_6O_7$). To a solution of 0.16 g (1 mmole) of 1-acetylbenzimidazole in 5 ml of chloroform was added a solution of 0.37 g (1.5 mmole) of PHA in 15 ml of chloroform. The mixture was agitated for 1 h at 55-60°C and, after cooling, the precipitate of picrate IIIc was filtered off. Yield 0.26 g (72%); bright yellow crystals with mp 220-223°C (ethanol) (literature: 223-226°C [14]). IR spectrum: 3330, 3220 (NH_2), 1610 cm^{-1} (C=N). PMR spectrum (DMSO-d_6); 6.83 (br. s, 2H, NH_2), 7.64 (m, 2H, 5-H, 6-H), 7.85 (m, 2H, 4-H, 7-H), 8.59 (s, 2H, 3'-H, 5'-H), 9.61 ppm (d, 1H, 2-H, J_{CH-NH} = 7.62 Hz).

1-Aminoimidazolium Picrate (IVc, $C_9H_8N_6O_7$). To a solution of 0.18 g (1.7 mmole) of 1-acetylimidazole in 5 ml of chloroform was added a solution of 0.6 g (2.5 mmole) of PHA in 20 ml of chloroform. The mixture was agitated for 1 h at 55-60°C and the precipitate of picrate IVc was then filtered off. Yield 0.44 g (84%); yellow crystals with mp 167-168°C (ethanol). IR spectrum: 3345, 3170, (NH_2), 1610 cm^{-1} (C=N). PMR spectrum (DMSO-d_6): 6.83 (br. s, 2H, NH_2), 7.62 (m, 2H, 4-H, 5-H), 8.59 (s, 2H, 3'-H, 5'-H), 9.08 ppm (m, 1H, 2-H); J_{2-H-NH} = 2.93 Hz, $J_{2-H-4(5)-H}$ = 1.47 Hz.

1-Amino-3-methoxymethylperimidinium Picrate (X, $C_{19}H_{16}N_6O_8$). This was obtained in a similar manner to picrate IIIa from 1.42 g (6.7 mmole) of 1-methoxymethylperimidine and 1.75 g (7.2 mmole) of PHA. The reaction was carried out at room temperature. Yield 2.6 g (85%); yellow crystals with mp 163-164°C (ethanol). IR spectrum: 3310, 3154 (NH_2), 1630 cm^{-1} (C=N), PMR spectrum (DMSO-d_6): 3.46 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 6.37 (br. s, 2H, NH_2), 7.10 (d, 1H, 9-H, J_{8-9} = 7.6 Hz), 7.20 (d, 1H, 4-H, J_{4-5} = 7.03 Hz), 7.55 (m, 4H, 5-H to 8-H), 8.58 (s, 2H, 3'-H, 5'-H), 9.20 ppm (s, 1H, 2-H).

Hydrolysis of Salt X. Picrate X (0.62 g; 1.36 mmole) was refluxed with 5 ml of conc. HCl for 10 min (for heating over a longer period a considerable quantity of tar was formed). The mixture was evaporated to dryness under reduced pressure, 6 ml of acetic acid and 0.14 ml (1.36 mmole) of benzaldehyde were added to the residue, and the mixture was refluxed for 1.5 h. The reaction mixture was concentrated down to 1/3 of its volume, diluted with 1 ml of water, neutralized with concentrated ammonia solution to pH 7, and again evaporated to dryness. The dry residue was extracted with 10 ml of warm chloroform and the extract was passed through an Al_2O_3 column (l = 20 cm, d = 1.5 cm), eluted with chloroform, and the orange fraction with R_f 0.83 was collected. Yield 0.02 g (5% based on picrate X) of 1-benzylidenaminoperimidine (XII), mp 172-174°C (in agreement with [7]).

1-Amino-2-cyanomethylbenzimidazole (XV, C_9H_8N). A. To a solution of 1.99 g (10 mmole) of 1-acetyl-2-cyanomethylbenzimidazole [15] in 20 ml of dichloromethane cooled to 0°C was added 2.71 g (10 mmole) of 90% PHA in a single batch. The mixture was agitated for 1 h at room temperature and the pale yellow crystalline precipitate (2.91 g) was then filtered off. The precipitate was dissolved on heating in 50 ml of 10% HCl and clarified with activated carbon (0.3 g), and the picric acid was then separated off by extraction with benzene (3 × 10 ml). The aqueous layer was made alkaline with solid potassium carbonate and the reaction product was extracted with dichloromethane (3 × 10 ml). Yield 0.29 g (17%) of amine XV as light straw-colored crystals with mp 144-145°C (from a 2:1 benzene–dichloroethane mixture). IR spectrum: 3394, 3195 (NH_2), 2247 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$): 4.06 (s, 2H, CH_2), 4.77 (br. s, 2H, NH_2), 7.23-7.38 (m, 3H, 5-H to 7-H), 7.71 ppm (m, 1H, 4-H).

The filtrate remaining after separation of the 2.91 g of precipitate was passed through an Al_2O_3 column (l = 12 cm, d = 4 cm). The lemon-yellow fraction was collected, yielding after evaporation 0.42 g (15.5%) of picryl acetate with mp 73-95°C.

B. A solution of 2.7 g (10 mmole) of 80% mesitylsulfonyl-O-hydroxylamine dried over sodium sulfate for 1 h at 0°C in 30 ml of dry diethyl ether was added in a single batch to 1.57 g (10 mmole) of 2-cyanomethylbenzimidazole powder (XVI). The mixture was agitated at room temperature for 1 h and the ocher-colored precipitate (2.81 g) was then separated. The precipitate was recrystallized from 50 ml of water using activated carbon (solution not heated above 90°C). Yield 1.58 g (42.5%); yellowish, needle-shaped crystals of 1-amino-2-cyanomethylbenzimidazolium mesitylsulfonate (XVII). This was treated with 10 ml of a saturated solution of potassium carbonate, base XV was extracted with dichloromethane (3 × 10 ml), and the extract was dried over sodium sulfate. After the dichloromethane was removed by evaporation under reduced pressure, 0.54 g (31%) of compound XV was obtained, having identical properties to the product obtained by method A.

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