TRANSFORMATIONS OF N-HETEROARYLFORMAMIDINES.

A NOVEL SYNTHESIS OF IMIDAZO/2,1-b/THIAZOLE AND IMIDAZO/2,1-b//1,3,4/THIADIAZOLE DERIVATIVES

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Abstract - Substituted imidazo/2,1-b/thiazole and imidazo/2,1-b//1,3,4/thiadiazole derivatives 3 and 9 were prepared from the corresponding thiazolylformamidine 2 by quaternization with phenacyl bromide and from the corresponding quaternized amino substituted 1,3,4-thiadiazole derivative 8 by treatment with DMFDMA, followed by cyclization and subsequent elimination of dimethylamine. This method represents a novel method for the preparation of imidazoazoles with a bridgehead nitrogen atom.

The most commonly used method for the synthesis of fused imidazoles is the alkylation of heterocyclic amines, having an amino group at the α-position in respect to the ring nitrogen atom, with α-halo carbonyl or related compounds.[1,2] There are several approaches for the preparation of imidazo/2,1-b/thiazole system known in the literature, either by cyclization of an imidazo-2(1H)-thione derivative with an α-halo carbonyl compound,[3-6] or by cyclization of a 2-aminothiazole derivative with an α-halo carbonyl compound.[7-9] Similarly, imidazo/2,1-b//1,3,4/thiadiazole system has been previously prepared by cyclization of 2-aminothiadiazole either with phenacyl bromide or bromoacetone.[10,11]

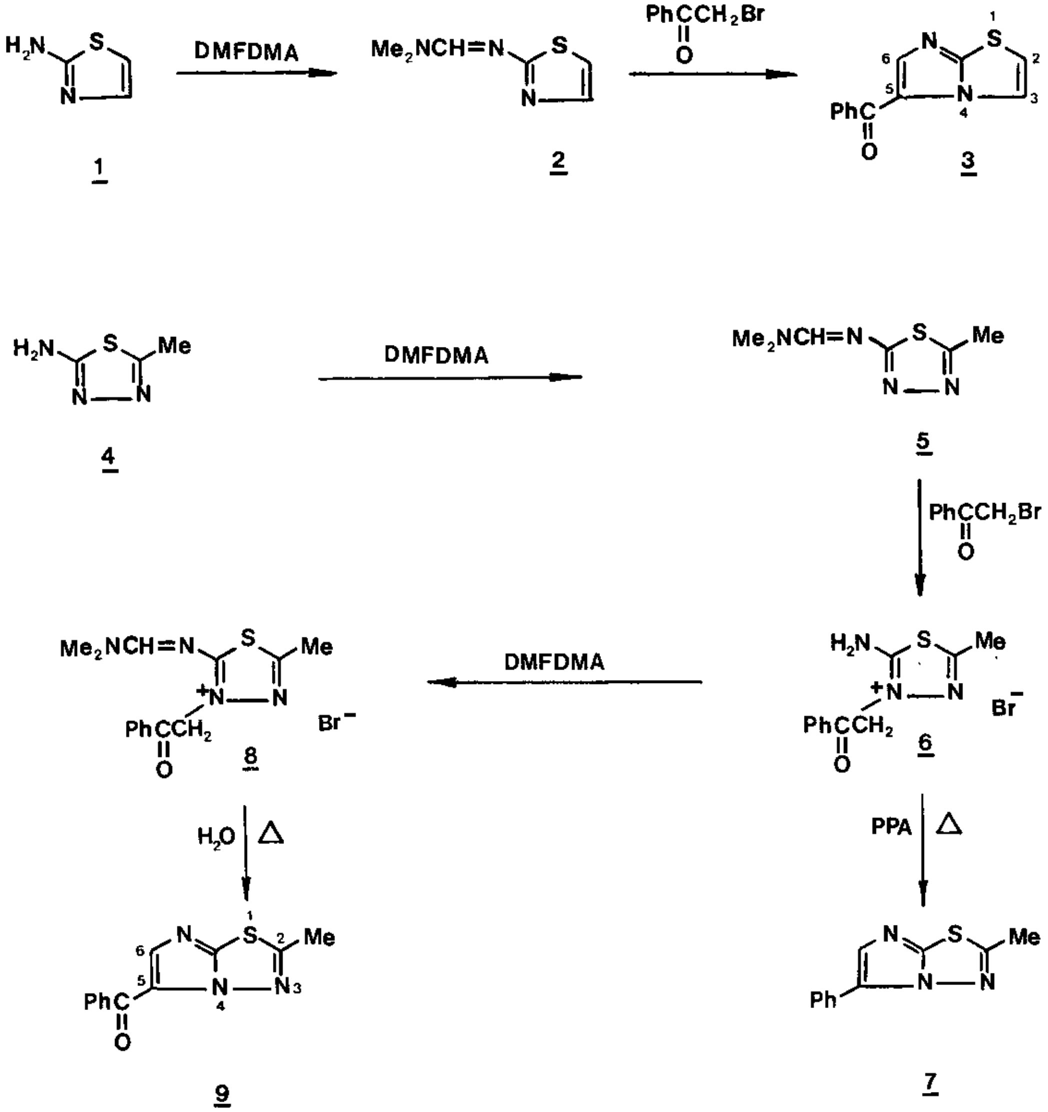
Recently, we reported a new synthesis of 3-acyl-substituted derivatives of imidazoazines with a bridgehead nitrogen atom from N-heteroarylformamidines, with the formamidine group attached at α-position in respect to the ring nitrogen atom, by quaternization with α-halo ketones followed by cyclization of the resulting quaternary salts.[2,11]

In this communication we report on a new approach to the synthesis of fused imidazoles in which the imidazole ring is fused to the five membered ring, as an extension of our research about the transformations of N-heteroarylformamidines and formamide oximes.[13]

Treatment of 2-(N,N-dimethylaminomethyleneamino)-thiazole (2) obtained from the corresponding 2-aminothiazole (1) and N,N-dimethylformamide dimethyl acetal (DMFDMA), with phenacyl bromide afforded 3-benzoylimidazo/2,1-b/thiazole (3). On the other hand, 2-(N,N-dimethylaminomethyleneamino)-5-methyl-1,3,4-thiadiazole (5) obtained from 2-amino-5-methyl-1,3,4-thiadiazole (4) and DMFDMA, gave by treatment with phenacyl bromide 2-amino-5-methyl-3-phenacyl-1,3,4-thiadiazolium bromide (6), identical with an authentic sample prepared from 2-amino-5-methyl-1,3,4-thiadiazole according to the known procedure.[10] The compound 6 was further transformed by heating in PPA into 2-methyl-6-phenylimidazo/2,1-b//1,3,4/thiadiazole (7) identical with an authentic samples prepared from 2-amino-5-methyl-1,3,4-thiadiazole according to the known procedure.[10] This indicates that quaternization of 2-(N,N-dimethylaminomethyleneamino)-5-methyl-1,3,4-thiadiazole (5) is taking place at nitrogen at position 3 next to the formamidine group. However, when 2-amino-5-methyl-3-phenacyl-1,3,4-thiadiazolium bromide (6) was treated with DMFDMA the corresponding 2-(N,N-dimethylaminomethyleneamino)-5-methyl-3-phenacyl-1,3,4-thiadiazolium bromide (8), isolated in the form of its hydrobromide, was formed. When this compound was heated in water cyclodehydration occurred to produce the corresponding 5-benzoyl-2-methylimidazo/2,1-b//1,3,4/thiadiazole (9). (Scheme 1).

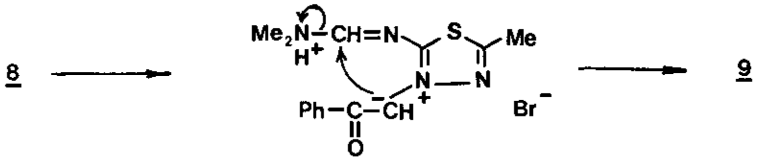
In this reaction C_6 is introduced by the acetal used for the preparation of the amidine, while C_5 and COPh group is introduced by the α-halo ketone used for quaternization. In the case of six-membered heterocycles cyclization is taking place with extreme easiness, so that we were not able to isolate the corresponding quaternary salts as intermediates.[2]

On the other hand, by treatment of 1,3,4-thiadiazole derivative 6 with phenacyl bromide the corresponding quaternary salt 8 was isolated, indicating that quaternary salt is indeed an intermediate. By further heating in aqueous solution the compound 8 cyclized by 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, afforded the imidazo/2,1-b//1,3,4/thiadiazole derivative 9. (Scheme 2).

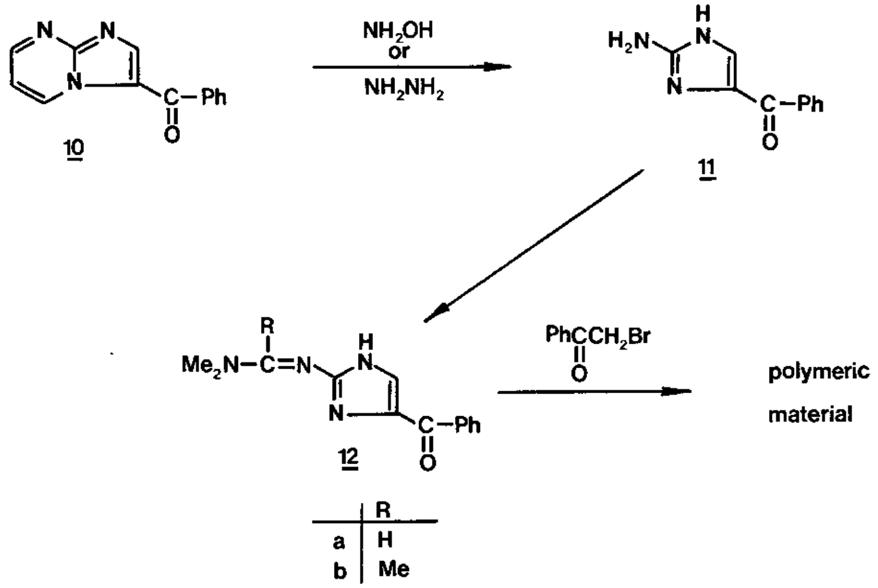


Scheme 1

On the other hand, 2-amino-5-benzoylimidazole (11), prepared from 3-benzoylimidazo /1,2-a/pyrimidine (10)[2], was transformed with DMFDMA into the corresponding formamidine derivative 12a and with N,N-dimethylacetamide dimethyl acetal into the corresponding acetamidine derivative 12b. However, treatment of these two imidazole derivatives with phenacyl bromide resulted only in a dark polymeric material. (Scheme 3).



Scheme 2



Scheme 3

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^1H nmr spectra were obtained on a JEOL JNM C60-HL spectrometer with TMS as internal standard, ir spectra on PERKIN-ELMER instrument 727B, mass spectra on a HITACHI-PERKIN-ELMER mass spectrometer RMU-6L, and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyser 240C.

5-Benzoylimidazo/2,1-*b*/thiazole (3). - A mixture of 1 (200 mg) and DMFDMA (0.3 ml) in toluene (5 ml) was heated under reflux (2h). The solvent was evaporated *in vacuo* to give 2. This was without purification used in further synthesis. Phenacyl bromide (420 mg) in toluene (5 ml) was added to the residue and the mixture was heated under reflux (2 h). The solvent was evaporated in vacuo. The oily residue crystallized after addition of n-propanol (3 ml). The solid was collected by suction to give 3 in 10 % yield, mp 148-150°C (from a mixture of cyclohexane and chloroform), m/e 228 (M^+, 100 %), nmr ($CDCl_3$/TMS) δ : 7.0 (dd, H_6), 7.30-7.60 (m) and 7.65-7.95 (m) (Ph, H_2), 8.40 (d, H_5), J_{H_5,H_6} 4.5 Hz, J_{H_2,H_6} 1.0 Hz. Anal.Calcd.for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27. Found: C, 62.75; H, 3.54; N, 12.26.

2-(*N*,*N*-Dimethylaminomethyleneamino)-5-methyl-1,3,4-thiadiazole (5). - A mixture of 4 (115 mg) and DMFDMA (0.3 ml) in toluene (5 ml) was heated under reflux (2 h). The crystals were, after cooling, collected by suction to give 5 in quantitative yield, mp 82-83°C (from cyclohexane), m/e 170 (M^+, 100 %), nmr ($CDCl_3$/TMS) δ : 2.45 (s, 5-Me), 2.90 (s) and 2.95 (s) (NMe_2), 8.10 (s, CH N).
Anal.Calcd.for $C_6H_{10}N_4S$: C, 42.33; H, 5.92; N, 32.91. Found: C, 42.24; H, 5.98; N, 32.98.

2-Amino-5-methyl-3-phenacyl-1,3,4-thiadiazolium bromide (6). - A mixture of 5 (170 mg) and phenacyl bromide (220 mg) in chloroform (5 ml) was heated under reflux (2 h). The solvent was evaporated in vacuo, the residue dissolved in water (10 ml), neutralized with solid sodium hydrogen carbonate and extracted with chloroform (3 times, 15 ml each time). The combined extracts were dried over anhydrous sodium sulphate to give (after evaporation of the solvent *in vacuo*) 6 in 60 % yield, mp 241-143°C, m/e 233 (M^+- HBr, 100 %), nmr (DMSO-d_6/TMS) δ: 2.50 (s, 5-Me), 6.00

(s, CH_2), 7.45-7.75 (m) and 7.85-8.10 (m) (Ph), 9.95 (br s, NH_2). Anal.Calcd. for $C_{11}H_{12}BrN_3OS$: C, 42.05; H, 3.85; N, 13.37. Found: C, 41.78; H, 3.78; N, 13.22.

2-Methyl-6-phenylimidazo/2,1-b//1,3,4/thiadiazole (7). - A mixture of 6 (628 mg) and PPA (5 g) was heated at 70°C (5 h). Crushed ice (20 g) was added, and the precipitate collected by suction to give 7 in quantitative yield, mp 135-137°C (from a mixture of ethanol and water), lit.[10] mp 137-138°C, nmr ($CDCl_3$/TMS) δ : 2.63 (s, 2-Me), 7.20-7.45 (m) and 7.65-7.80 (m) (Ph), 7.85 (s, H_5).

2-(N,N-Dimethylaminomethyleneamino)-5-methyl-3-phenacyl-1,3,4-thiadiazolium bromide monohydrate (8). - A mixture of 6 (314 mg) and DMFDMA (3 ml) was stirred at room temperature (24 h). The precipitate was collected by suction to give 9 in 80 % yield, mp 197-199°C, nmr (DMSO-d_6/TMS) δ : 2.60 (s, 5-Me), 3,05 (s) and 3.55 (s) (NMe_2), 5.70 (s, CH_2), 7.45-7.70 (m) and 7.85-8.10 (m) (Ph), 9.60 (s, CH=N). Anae.Calcd. for $C_{14}H_{17}BrN_4OS$: C, 43.42; H, 4.94; N, 14.47. Found: 43.77; H, 4.46; N, 14.16.

5-Benzoyl-2-methylimidazo/2,1-b//1,3,4/thiadiazole (9). - A solution of 2-(N,N-dimethylaminomethyleneamino)-5-methyl-3-phenacyl-1,3,4-thiadiazolium bromide 8 (369 mg) in water (1 ml) was heated under reflux (1h). The precipitate was, after cooling,collected by suction to give the compound 9 in 50 % yield, mp 126-129°C (from water).

Anal. Calcd. for $C_{12}H_9N_3OS$. H_2O; C, 55.16; H, 4.24; N, 16.08. Found: C, 55.35; H, 4.22; N, 16.01.

2-Amino-4-benzoylimidazole (11). - a) A mixture of 3-benzoylimidazo/1,2-a/pyrimidine (10)[2] (225 mg) and hydrazine hydrate (80 %, 60 mg) in ethanol (5 ml) was heated under reflux (2 h). The crystals were, after cooling, collected by suction to give the compound (11) in 81 % yield, mp 228°C (decomp.) (from water), m/e 187 (M^+, 100 %), nmr (DMSO-d_6/TMS) δ : 6.10 (br s, NH_2), 7.30 (s, H_5), 7.40-7.70 (m) and 7.70-7.95 (m) (Ph), 11.15 (br s, NH).

Anal.Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.82; H, 4.94; N, 22.39.

b) A mixture of 3-benzoylimidazo/1,2-a/pyrimidine (10) (223 mg) and hydroxylamine (100 mg) in ethanol (5 ml) was heated under reflux (1 h). The solvent was evaporated in vacuo, water (5 ml) was added to the residue and the solid was collected by suction to give the compound 11 in 75 % yield, mp 228°C (from water). The ir spectrum of the compound was identical with that of the compound described under a).

4-Benzoyl-2-(N,N-dimethylaminomethyleneamino)-imidazole (12a). - A mixture of 2-amino-4-benzoylimidazole (11) (187 mg) and DMFDMA (145 mg) in toluene(65 ml) was heated under reflux (2 h). The solid was, after cooling, collected by suction to give the compound 12a in 85 % yield, mp 191-193°C (from toluene), m/e 242 (M^+,100 %), nmr ($CDCl_3$/TMS) δ : 2.95 (s) and 3.06 (s) (NMe_2), 7.30-7.55 (m) and 7.70-7.90 (m) (Ph), 8.65 (s, H_5), 9.90 (br s, NH).
Anal.Calcd. for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82 ; N, 23,12. Found: C, 64.79; H, 6.01; N, 22.97.

4-Benzoyl-2-(N,N-dimethylaminoethylideneamino)-imidazole (12b). - A mixture of 2-amino-4-benzoylimidazole (11) (187 mg) and DMADMA (150 mg) in toluene (5 ml) was heated under reflux (2 h). The crystals were, after cooling, collected by suction to give the compound 12b in 50 % yield, mp 139-142°C (from toluene), m/e 256 (M^+, 100 %), nmr ($CDCl_3$/TMS) δ : 2.35 (s, C-Me), 3.05 (s, NMe_2), 7.35-7.55 (m) and 7.75-7.85 (m) (Ph, H_5), 8.70 (br s, NH).
Anal.Calcd. for $C_{14}H_{16}N_4O$: C, 69.51; 6.67; N, 18.53; Found: C, 69.30; H, 6.78; N, 18.88.

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REFERENCES AND NOTES

1. For reviews see: a) J.P.Paolini in: Special Topics in Heterocyclic Chemistry, A. Weissberger, E.C.Taylor, Eds., John Wiley and Sons, New York, 1977, 1-115.

b) G.Maury in : Special Topics in Heterocyclic Chemistry, A.Weisberger, E.C. Taylor, Eds., John Wiley and Sons, New York, 1977, pp 179-244.

2. S.Podergajs, B.Stanovnik, and M.Tišler, *Synthesis*, 1984, 263, and references cited therein.
3. H.Andersag and K.Westphal, *Chem.Ber.*, 1954, **70B**, 2035.
4. E.Ochiai, *Ber*. 1936, **69B**, 1650.
5. E.Ochiai and F.YÜ Hou, *J.Pharm.Soc.Japan*, 1938, **58**, 236; *Chem.Abstr.*, 1938, **32**, 4161.
6. A.Lawson and H.V.Morley, *J.Chem.Soc.*, 1957, 566.
7. L.M.Werbel and M.L.Zamora, *J.Heterocyclic Chem.*, 1965, **2**,287.
8. H.Kondo and F.Nagasawa, *J.Pharm.Soc.Japan*, 1937, **57**, 1050; *Chem.Abstr.*,1938, **32**, 3398.
9. L.Almirante, A.Mugnaini, and L.Polo Fritz, and E.Provinciali, *Boll.Chim.Farm.*, 1966, **105**, 32; *Chem.Abstr.*, 1966, **65**, 699.
10. T.Matsukawa and S.Ban, *J.Pharm.Soc.Japan*, 1952, **72**, 610; *Chem.Abstr.*, 1953, **47**, 6409.
11. S.Ban, *J.Pharm.Soc.Japan*, 1954, **74**, 658; *Chem.Abstr.*, 1954, **48**, 10741.
12. S.Fajgelj, B.Stanovnik, and M.Tišler, *Vestn.Slov.Kem.Drus.*, 1985, **32**, 137.
13. For reviews see: a) B.Stanovnik, *Chemicke Zvesti (Chemical Papers)*,1982, **36**, 693.
    b) M.Tišler, *Heterocycles*, 1983, **20**, 1591.

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