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Tetrazoles: XLV.* Amidoalkylation of 5-Substituted Tetrazoles

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Abstract—Amidoalkylation of 5-aryl(hetaryl)tetrazoles with *N*-hydroxymethylamides of aliphatic and aromatic carboxylic acids occurs regioselectively and yields mainly 5-aryl(hetaryl)-2-acylaminomethyltetrazoles. These compounds are fairly stable in neutral media but are smoothly deprotected by the action of aqueous sodium hydroxide or hydrochloric acid.

Development of procedures for protection of the N–H bond in tetrazoles is one of the most important problems in the chemistry of these compounds. This is explained by the fact that in most cases protection of the N–H bond is a key stage in such processes as functionalization of 5-substituted tetrazoles [2, 3] and synthesis of tetrazole-containing substrates which are widely used as medicines [4, 5].

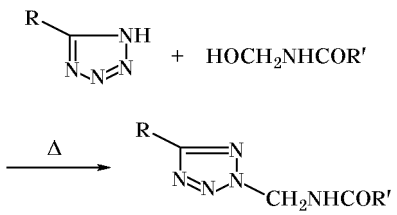
The problem is especially important in the synthesis of drugs, where the protective group should remain unchanged at all stages of multistep synthesis, and in the final stage it should be readily removed under mild conditions, under which the other functional groups are not involved.

Among numerous N–H-protecting groups [6, 7], the following are used in the chemistry of tetrazoles: benzyloxymethyl [3, 8], dimethyl(phenyl)methyl [9], triphenyl (trityl) [1, 2, 10], and 4,4′-dimethoxytriphenylmethyl [11]. Most authors believe that the trityl group whose protective action is based mainly on steric effect is preferred.

While studying methods for protection of N–H bond in tetrazoles, we estimated the possibility of using amidomethyl group for this purpose. Only two examples have been reported on introduction of amidomethyl group into tetrazole ring. We previously showed that treatment of 5-nitrotetrazole with *N*-hydroxymethylamides of aliphatic and aromatic carboxylic acids gives the corresponding 2-acylaminomethyl-5-nitrotetrazoles [12]. Analogous results were obtained in the amidoalkylation of 5-phenyltetrazole with *N*-hydroxymethylbenzamide [13].

We have found that 5-aryl(hetaryl)tetrazoles react with *N*-hydroxymethyl aliphatic and aromatic carboxylic acid amides to afford the corresponding *N*-tetrazolylmethylamides **Ia**–**Io** (Scheme 1). The reaction occurs at 120°C in the absence of a solvent. Only in the synthesis of tetrazole **Io**, the reaction was carried out in dimethylformamide to increase the solubility of the reactants.

Scheme 1.



Ia–Io

I, R′ = Me, R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-ClC_6H_4 (**c**), 4-$NO_2C_6H_4$ (**d**), 2-furyl (**e**), 4-pyridyl (**f**); R′ = CH_2Cl, R = Ph (**g**); R′ = $(CH_2)_2CH_3$, R = 4-$MeOC_6H_4$ (**h**), 4-ClC_6H_4 (**i**), 4-FC_6H_4 (**j**), 4-pyridyl (**k**); R′ = Ph, R = Ph (**l**), 4-$MeOC_6H_4$ (**m**), 4-ClC_6H_4 (**n**), 4-piridyl (**o**).

It is important that the amidoalkylation of 5-substituted tetrazoles is characterized by a high regioselectivity. According to the ^1H NMR data, the ratio of isomeric 1- and 2-acylaminomethyltetrazoles is ~1 : 10. Presumably, the reason is that the reactive species in the amidoalkylation process is iminocarbenium ion $\overset{+}{C}H_2{=}NCOR$ [14].

2-Acylaminomethyltetrazoles **Ia**–**Io** are relatively stable in neutral medium. However, they are smoothly deprotected to the corresponding 5-substituted tetra-

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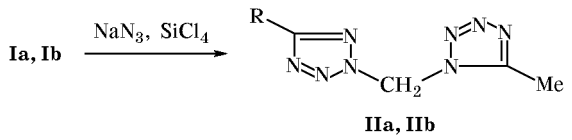
zoles by the action of 10% aqueous sodium hydroxide or 10% hydrochloric acid.

2-Acylaminomethyltetrazoles can be used in the synthesis of complex systems including two tetrazole rings. In the synthesis of 1,5-disubstituted tetrazoles from monosubstituted carboxylic acid amides, the latter are usually treated in succession with phosphorus pentachloride and hydrazoic acid [15] or sodium azide (when the reaction is carried out under phase-transfer conditions [16]). Taking into account the sensitivity of 2-acylaminomethyltetrazoles to acids, the above procedure is inapplicable. We have synthesized bis-tetrazoles **IIa** and **IIb** in a satisfactory yield by reaction of 2-acylaminomethyltetrazoles **Ia** and **Ib** with sodium azide in the presence of silicon tetrachloride (Scheme 2).

Scheme 2.



II, R = Ph (**a**), 4-$MeOC_6H_4$ (**b**).

The procedure is very simple, and (what is very important) the other functional groups present in the substrate remain intact [17].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples pelleted with KBr. The ^1H and ^{13}C NMR spectra were measured on a Bruker AC-200 instrument in DMSO-d_6.

2-Acetylaminomethyl-5-phenyltetrazole (Ia). A mixture of 0.017 mol of acetamide, 0.016 mol of paraformaldehyde, and 0.001 g of sodium hydroxide was heated for 15–20 min at 120°C. 5-Phenyltetrazole, 0.014 mol, was added, and the mixture was heated for 20 min at 110–120°C and was left to stand for 24 h. It was then treated with water (2 × 20 ml), and the precipitate was filtered off. Yield 2.3 g (79%), mp 99°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 940, 990, 1020, 1050, 1080, 1130, 1190, 1270, 1350, 1380, 1460, 1550, 1710, 2870, 2940, 2990, 3030, 3330. ^1H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 5.91–5.95 d (2H, CH_2), 7.4–7.6 m (3H, H_{arom}), 8.0–8.1 m (2H, H_{arom}), 9.36–9.42 t (1H, NH). Found, %: C 55.47; H 4.99; N 32.30. $C_{10}H_{11}N_5O$. Calculated, %: C 55.30; H 5.07; N 32.26.

Compounds **Ib**–**In** were synthesized by a similar procedure.

2-Acetylaminomethyl-5-(4-methoxyphenyl)tetrazole (Ib). Yield 94%, mp 145°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 840, 1020, 1040, 1115, 1180, 1270, 1310, 1330, 1350, 1380, 1400, 1430, 1450, 1475, 1560, 1620, 1680, 2865, 2940, 2990, 3080, 3330. ^1H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 3.83 s (3H, OCH_3), 5.88–5.91 d (2H, CH_2), 7.04–7.08 d (2H, H_{arom}), 7.95–8.0 d (2H, H_{arom}), 9.3–9.34 t (1H, NH). Found, %: C 53.42; H 5.51; N 28.29. $C_{11}H_{13}N_5O_2$. Calculated, %: C 53.44; H 5.26; N 28.34.

2-Acetylaminomethyl-5-(4-chlorophenyl)tetrazole (Ic). Yield 86%, mp 143°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 850, 1000, 1050, 1100, 1110, 1185, 1300, 1440, 1455, 1500, 1555, 1620, 1680, 2850, 2945, 3090, 3325. ^1H NMR spectrum, δ, ppm: 1.93 s (3H, CH_3), 5.95–5.97 d (2H, CH_2), 7.63–7.66 m (3H, H_{arom}), 8.05–8.08 m (2H, H_{arom}), 9.3–9.4 t (1H, NH). Found, %: C 47.76; H 4.08; N 27.76. $C_{10}H_{10}ClN_5O$. Calculated, %: C 47.71; H 3.98; N 27.83.

2-Acetylaminomethyl-5-(4-nitrophenyl)tetrazole (Id). Yield 97%, mp 171°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 790, 860, 880, 1010, 1040, 1110, 1135, 1185, 1220, 1295, 1350, 1435, 1470, 1530, 1610, 1685, 2870, 2940, 3090, 3110, 3290. ^1H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 5.8–5.9 d (2H, CH_2), 8.3–8.4 m (4H, H_{arom}), 9.3–9.4 t (1H, NH). Found, %: C 45.94; H 3.73; N 32.09. $C_{10}H_{10}N_6O_3$. Calculated, %: C 45.80; H 3.82; N 32.06.

2-Acetylaminomethyl-5-(2-furyl)tetrazole (Ie). Yield 62%, mp 115°C (from water). IR spectrum, ν, cm^{-1}: 920, 1010, 1060, 1130, 1190, 1240, 1300, 1380, 1440, 1520, 1560, 1570, 1640, 1680, 2870, 2940, 2990, 3140, 3310. ^1H NMR spectrum, δ, ppm: 1.91 s (3H, CH_3), 5.91–5.95 d (2H, CH_2), 6.72 s (1H, furyl), 7.17–7.18 d (1H, furyl), 7.93 s (1H, furyl), 9.3–9.4 t (1H, NH). Found, %: C 46.42; H 4.33; N 33.89. $C_8H_9N_5O_2$. Calculated, %: C 46.38; H 4.35; N 33.81.

2-Acetylaminomethyl-5-(4-pyridyl)tetrazole (If). Yield 65%, mp 127°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 850, 1010, 1050, 1125, 1220, 1290, 1340, 1380, 1430, 1470, 1540, 1560, 1620, 1700, 3070, 3220, 3530. ^1H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 5.95–5.99 d (2H, CH_2), 7.95–7.98 m (2H, H_{arom}), 8.74–8.76 m (2H, H_{arom}), 9.3–9.4 t (1H, NH). Found, %: C 49.59; H 4.65; N 38.63. $C_9H_{10}N_6O$. Calculated, %: C 49.54; H 4.59; N 38.53.

2-Chloroacetylaminomethyl-5-phenyltetrazole (Ig). Yield 59%, mp 95–97°C (from ethyl acetate). IR spekctrum, ν, cm^{-1}: 900, 930, 1010, 1040, 1050, 1070, 1110, 1220, 1280, 1350, 1410, 1460, 1480, 1550, 1670, 1700, 2860, 2940, 2980, 3030, 3090, 3320. ^1H NMR spectrum, δ, ppm: 4.15 s (2H, CH_2), 5.99–6.02 d (2H, CH_2), 7.51–7.54 m (3H, H_{arom}), 8.04–8.07 m (2H, H_{arom}), 9.71 s (1H, NH). Found, %: C 47.70; H 4.01; N 27.80. $C_{10}H_{10}ClN_5O$. Calculated, %: C 47.71; H 3.98; N 27.83.

2-Butyrylaminomethyl-5-(4-methoxyphenyl)-tetrazole (Ih). Yield 77%, mp 109–110°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 840, 1030, 1180, 1190, 1220, 1260, 1295, 1350, 1400, 1440, 1480, 1550, 1620, 1670, 2960, 2990, 3020, 3300. ^1H NMR spectrum, δ, ppm: 0.86–0.94 t (3H, CH_3), 1.57–1.69 m (2H, CH_2), 2.23–2.30 t (2H, CH_2), 3.88 s (3H, OCH_3), 6.04–6.07 d (2H, CH_2), 7.07–7.11 d (2H, H_{arom}), 8.02–8.07 d (2H, H_{arom}), 8.49 s (1H, NH). Found, %: C 56.82; H 6.09; N 25.41. $C_{13}H_{17}N_5O_2$. Calculated, %: C 56.73; H 6.18; N 25.45.

2-Butyrylaminomethyl-5-(4-chlorophenyl)tetrazole (Ii). Yield 71%, mp 141°C (from ethyl acetate–petroleum ether, 1:1). IR spectrum, ν, cm^{-1}: 840, 1020, 1040, 1100, 1185, 1210, 1220, 1350, 1390, 1420, 1440, 1470, 1550, 1610, 1680, 2890, 2950, 2980, 3350. ^1H NMR spectrum, δ, ppm: 0.86–0.94 t (3H, CH_3), 1.58–1.69 m (2H, CH_2), 2.24–2.31 t (2H, CH_2), 6.08–6.11 d (2H, CH_2), 7.58–7.62 d (2H, H_{arom}), 8.01–8.14 d (2H, H_{arom}), 8.53 s (1H, NH). Found, %: C 51.46; H 5.05; N 25.10. $C_{12}H_{14}ClN_5O$. Calculated, %: C 51.52; H 5.00; N 25.04.

2-Butyrylaminomethyl-5-(4-fluorophenyl)tetrazole (Ij). Yield 47%, mp 67–69°C (from hexane). IR spectrum, ν, cm^{-1}: 850, 1040, 1100, 1170, 1190, 1220, 1240, 1320, 1430, 1470, 1560, 1610, 1680, 2890, 2930, 2960, 2980, 3080, 3300. ^1H NMR spectrum, δ, ppm: 0.86–0.94 t (3H, CH_3), 1.54–1.67 m (2H, CH_2), 2.20–2.31 t (2H, CH_2), 6.07–6.10 d (2H, CH_2), 7.29–7.37 t (2H, H_{arom}), 8.10–8.19 m (2H, H_{arom}), 8.53 t (1H, NH). Found, %: C 54.56; H 5.45; N 26.50. $C_{12}H_{14}N_5OF$. Calculated, %: C 54.75; H 5.32; N 26.62.

2-Butyrylaminomethyl-5-(4-pyridyl)tetrazole (Ik). Yield 79%, mp 95–96°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 850, 1000, 1045, 1180, 1210, 1280, 1330, 1430, 1470, 1530, 1620, 1690, 1710, 2890, 2950, 2980, 3060, 3220, 3350. ^1H NMR spectrum, δ, ppm: 0.87–0.94 t (3H, CH_3), 1.58–1.69 m (2H, CH_2), 2.25–2.33 t (2H, CH_2), 6.13–6.16 d (2H, CH_2), 7.98–8.02 t (2H, H_{arom}), 8.57 t (1H, NH), 8.76–8.79 m (2H, H_{arom}). Found, %: C 53.58; H 5.66; N 34.27. $C_{11}H_{14}N_6O$. Calculated, %: C 53.66; H 5.69; N 34.15.

2-Benzoylaminomethyl-5-phenyltetrazole (Il). Yield 82%, mp 152°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 1040, 1050, 1170, 1180, 1210, 1310, 1335, 1390, 1420, 1460, 1480, 1500, 1550, 1670, 2860, 2940, 3090, 3240. ^1H NMR spectrum, δ, ppm: 6.12–6.15 d (2H, CH_2), 7.35–7.65 m (6H, H_{arom}), 7.9–8.1 m (4H, H_{arom}), 9.86 t (1H, NH). Found, %: C 64.70; H 4.47; N 24.99. $C_{15}H_{13}N_5O$. Calculated, %: C 64.52; H 4.66; N 25.09.

2-Benzoylaminomethyl-5-(4-chlorophenyl)tetrazole (Im). Yield 73%, mp 135°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 850, 1020, 1050, 1100, 1180, 1210, 1300, 1350, 1390, 1420, 1470, 1500, 1560, 1680, 2860, 2950, 3080, 3300. ^1H NMR spectrum, δ, ppm: 6.15–6.20 d (2H, CH_2), 7.45–7.6 m (6H, H_{arom}), 7.85–8.15 m (4H, H_{arom}), 9.85 t (1H, NH). Found, %: C 57.45; H 4.00; N 22.44. $C_{15}H_{12}N_5OCl$. Calculated, %: C 57.41; H 3.83; N 22.33.

2-Benzoylaminomethyl-5-(4-methoxyphenyl)-tetrazole (In). Yield 82 %, mp 142°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 840, 1030, 1190, 1260, 1300, 1310, 1450, 1480, 1500, 1550, 1630, 1670, 2860, 2940, 2990, 3025, 3070, 3350. ^1H NMR spectrum, δ, ppm: 3.83 s (3H, CH_3), 6.10–6.14 d (2H, CH_2), 7.03–7.07 m (2H, H_{arom}), 7.40–7.60 m (3H, H_{arom}), 7.90–8.00 m (4H, H_{arom}), 9.91 t (1H, NH). Found, %: C 62.16; H 4.79; N 22.81. $C_{16}H_{15}N_5O_2$. Calculated, %: C 62.14; H 4.85; N 22.65.

2-Benzoylaminomethyl-5-(4-pyridyl)tetrazole (Io). A mixture of 0.015 mol of benzamide, 0.012 mol of paraformaldehyde, and 0.001 g of sodium hydroxide in 10–15 ml of DMF was heated for 20 min at 120°C, and 0.01 mol of 5-(4-pyridyl)tetrazole was added. The mixture was then heated for 3 h at 110–120°C and evaporated on a water bath. Yield 89%, mp 188°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 850, 1010, 1050, 1180, 1290, 1430, 1470, 1500, 1570, 1620, 1630, 1690, 2860, 2940, 3040, 3270, 3450. ^1H NMR spectrum, δ, ppm: 6.15–6.22 d (2H, CH_2), 7.44–7.65 m (3H, H_{arom}), 7.9–8.0 m (4H, H_{arom}), 8.74–8.76 m (2H, H_{arom}), 10.00 t (1H, NH). Found, %: C 60.06; H 4.38; N 30.08. $C_{14}H_{12}N_6O$. Calculated, %: C 60.00; H 4.29; N 30.00.

5-Methyl-1-(5-phenyltetrazol-2-ylmethyl)tetrazole (IIa). A solution of 0.01 mol of silicon tetrachloride in 10 ml of acetonitrile was added to a mixture of 0.004 mol of tetrazole **Ia** and 0.008 mol of sodium azide in 20 ml of acetonitrile, placed in a reactor protected from atmospheric moisture. The mixture was heated for 6 h at 65–70°C, and additional

0.002 mol of sodium azide and 0.002 mol of silicon tetrachloride were added. This procedure was repeated every 6 h until the conversion of the initial tetrazole was complete. The mixture was cooled to 15°C and slowly poured into a 15% solution of sodium carbonate, maintaining the pH at 8. The product was extracted with ethyl acetate (2×50 ml), and the extract was evaporated under reduced pressure. Yield 1.2 g (61%), mp 174–176°C (decomp., from ethanol). IR spectrum, ν, cm^{-1}: 890, 910, 930, 1010, 1030, 1040, 1090, 1170, 1190, 1290, 1330, 1360, 1390, 1450, 1500, 1520, 1600, 2970, 3040, 3070. ^{1}H NMR spectrum, δ, ppm: 2.76 s (3H, CH_3), 7.51–7.58 m (5H, H_{arom}), 8.04–8.07 m (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 8.44, 59.49, 126.05, 126.57, 129.31, 131.05, 153.70, 165.00. Found, %: C 49.65; H 4.23; N 46.13. $C_{10}H_{10}N_8$. Calculated, %: C 49.59; H 4.13; N 46.28.

5-Methyl-1-[5-(4-methoxyphenyl)tetrazol-2-ylmethyl]tetrazole (IIb) was synthesized in a similar way. Yield 29%, mp 133–134°C (from ethanol). IR spectrum, ν, cm^{-1}: 910, 940, 1000, 1040, 1070, 1100, 1150, 1170, 1190, 1230, 1280, 1300, 1330, 1390, 1450, 1500, 1580, 1600, 2900, 2950, 2990, 3050. ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 3.82 s (3H, CH_3), 7.05–7.10 d (2H, H_{arom}), 7.45 s (2H, CH_2), 7.98–8.07 d (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 8.47, 55.23, 59.33, 114.50, 118.49, 128.17, 153.40, 161.29, 165.04. Found, %: C 48.55; H 4.18; N 40.53. $C_{11}H_{12}N_8O$. Calculated, %: C 48.52; H 4.41; N 41.17.

Acid hydrolysis of 2-acetylaminomethyl-5-phenyltetrazole (Ia). A mixture of 3.4 mmol of azole **Ia** and 10 ml of 10% hydrochloric acid was heated for 1 h at 60–70°C. The mixture was cooled, and the precipitate was filtered off. We thus obtained 0.47 g (95%) of 5-phenyltetrazole, mp 218°C [18].

Alkaline hydrolysis of 2-acetylaminomethyl-5-phenyltetrazole (Ia). A mixture of 3.4 mmol of azole **Ia** and 10 ml of a 10% solution of sodium hydroxide was heated for 1 h at 60–70°C. The mixture was cooled and acidified with 10% hydrochloric acid to pH 1, and the precipitate was filtered off to obtain 0.45 g (92%) of 5-phenyltetrazole, mp 218°C [18].

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