On the Preparation of 5-(α-Diazoethyl)tetrazoles

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Z. Naturforsch. **51b,** 1815–1817 (1996); received August 14, 1996

5-(α-Diazoethyl)tetrazoles, Methyl Tetrazol-5-yl Ketone Hydrazones, Silver(I) Oxide, Dehydrogenation

Hydrazone dehydrogenation with silver(I) oxide in the presence of sodium hydroxide was found an efficient approach to the title compounds, whereas application of the Bamford-Stevens reaction proved unsatisfactory.

In connection with rearrangement studies in the 1,2,3-triazole series [1] we needed authentic samples of certain 5-(α-diazoethyl)tetrazoles, *viz.* **1** and **5** and the anion of **9**. While detailed knowledge is available for preparing a wide variety of diazoalkanes [2], experience in making tetrazolyl-substituted types is limited. Known routes starting from tetrazoles as substrates include (*i*) diazo transfer [3] and – for (diazo*methyl*)tetrazoles – functional group transformation such as (*ii*) amine diazotization in weakly acidic media [4], (*iii*) the Bamford-Stevens reaction [1,4] and (*iv*) alkaline cleavage of *N*-alkyl-*N*-nitrosourethanes [4,5]. Application of method *i* requires either an additional activating substituent (usually an acyl group) or an enamine function, method *ii* should be ineffectual with **5** and **9**, and method *iv* requires an elaborate educt synthesis. We therefore attempted the short approach *iii*.

The requisite ketones **2**, **6** and **10** (precursors to the tosylhydrazones **3**, **7** and **11**) are readily available. As for **2** (a still unknown tetrazole), the straightforward sequence **13** → **14** → **15** → **2** based on standard procedures [6] was used. The isomer **6** could easily be made from the nitrile **17** (obtainable as major product by methylation of **16** [7]). This route was given preference over a literature method that starts from the carboxylic ester (**17**: CO_2Et in place of CN) [8], because in that case the educt (likewise made *via* ring methylation) was later shown to consist of an inseparable 1:1 mixture of 1- and 2-methyl isomers [7,9] and, hence, has been used impure [8]. For the ketone **10**, an expedient synthesis (akin to that shown for **6**) has lately been published [10].

When the tosylhydrazone **3** was treated in the manner described for the analogous aldehyde derivative [4], only traces of the desired diazo compound **1** (if any) were formed, although for this reaction the more favourable (*E*)-isomer of **3** was employed [11]. In the case of **11**, the variant that earlier proved effective with the ring-unsubstituted aldehyde congener [1] was tried [*i.e.*, brief heating (≤ 5 min) with DBN (1,5-diazabicyclo-[4.3.0]non-5-ene) in DMSO as solvent], but here too our efforts remained unrewarded. Since under these conditions also both **3** and **7** [the latter available in (*Z*)-form only] turned out to be unsuitable candidates, we converted the above ketones into the hydrazones **4**, **8** and **12** [12]. When these derivatives were treated with silver(I) oxide in the presence of sodium hydroxide, a smooth reaction occurred to produce the expected materials **1**, **5** and **9** in reasonable yield. We found that for a successful transformation **12** → **9** the *sodium* salt of **12** is required (rather than the hydrazinium salt which directly comes off the reaction mixture). While compounds **1** and **5** were isolated as yellow and orange solids, respectively, the species **9** was generated in solution only. Upon addition of methyl iodide to the latter, rapid formation of **1** and **5** was observed (ratio 1 : 2.3) [13]. In a supplementary experiment we checked the behaviour of the sodium salt of the tetrazolecarbaldehyde hydrazone (**12**: H in place of Me) [14]. In marked contrast to **9**, no diazo compound was obtained. This again shows the tremendous effect of even slight variations in educt structure [15].

Experimental [16]

1-(1-Methyltetrazol-5-yl)ethanol (**15**)

The tetrazole **14** (33.0 g, 225 mmol) – a colourless lachrymatory oil [17] obtained in 84% yield by application of the procedure given in ref. [6a] – was dissolved in acetic acid (225 ml) and after addition of anhydrous sodium acetate (36.9 g, 450 mmol) the mixture was refluxed for 16 h. Evaporation of the solvent, followed by addition of water, neutralization with $NaHCO_3$ and extraction with ether afforded a viscous oil (21.6 g) of

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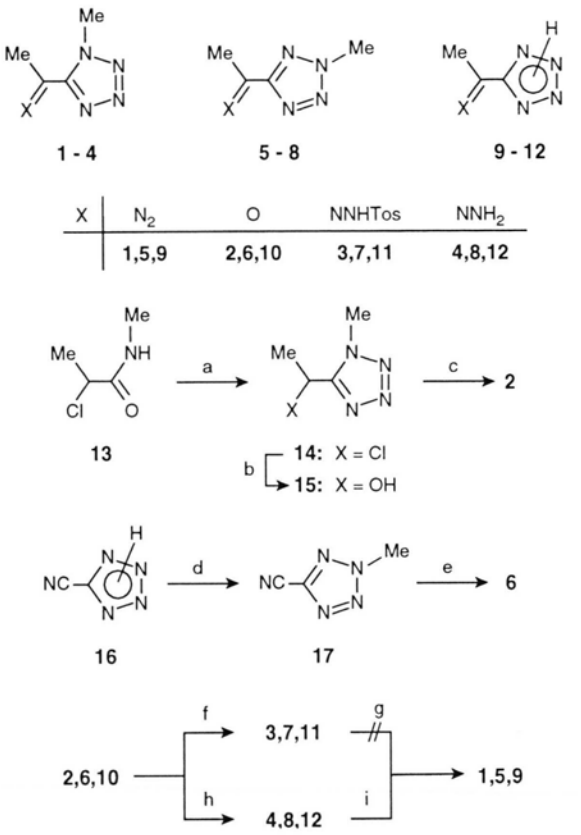
0932–0776/96/1200–1815 $06.00



Reagents: a = PCl_5, then HN_3; b = NaOAc, then HCl; c = $K_2Cr_2O_7$ / H_2SO_4; d = MeI / $NaHCO_3$ (see ref.[7]); e = MeMgI, then H_2SO_4; f = $TosNHNH_2$ / HCl; g = base / heat (see text); h = $NH_2NH_2 \cdot H_2O$; i = Ag_2O / NaOH (**12** as sodium salt, product **9** in tetrazolide form only).

which 15.5 g were dissolved in methanol / 12 N HCl (120 ml, 5 / 1) and then again heated at reflux for 3.5 h. Evaporation to dryness gave a residue that was recrystallized from ethyl acetate / light petroleum to yield 6.12 g (74%) of **15**; m.p. 56–57 °C. – IR (KBr): $\tilde{\nu}$ = 3250 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.67 (d, J = 7 Hz, 3 H, CH*Me*), 4.17 (s, 3 H, NMe), 4.20 (s, 1 H, OH, exchangeable with D_2O), 5.24 (q, J = 7 Hz, 1 H, C*H*Me).

Methyl (1-methyltetrazol-5-yl) ketone (**2**)

A vigorously stirred mixture of the tetrazole **15** (5.0 g, 39 mmol), $K_2Cr_2O_7$ (3.9 g, ca. 13 mmol) and 3 N H_2SO_4 (27 ml) was slowly heated to 80 °C and held at this temperature for 0.5 h. Extraction with ether and evaporation of the solvent gave **2** as a colourless, non-crystallizing oil; yield 3.46 g (70%). – IR (neat): $\tilde{\nu}$ = 1710 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.84 (s, 3 H, CMe), 4.34 (s, 3 H, NMe).

Methyl (2-methyltetrazol-5-yl) ketone (**6**)

To a boiling solution of methylmagnesium iodide (200 mmol) in anhydrous ether (200 ml) the nitrile **17** [10.9 g, 100 mmol; made from **16** [7], fraction used: b.p. 54–57 °C / 0.9 Torr, ^1H NMR ($CDCl_3$, δ) 4.53 (s)] was added dropwise and the mixture refluxed for 3 h. Workup by cautious addition of ice (200 g) and 7 N H_2SO_4 (400 ml), followed by extraction with ether (3 x 200 ml), concentration of the combined organic layers and filtration over silica gel (ethyl acetate as eluent) afforded the product which solidified on cooling; yield 5.70 g (45%); m.p. 38–41 °C (ref.[8] 41–42 °C). – IR (KBr): $\tilde{\nu}$ = 1715 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.78 (s, 3 H, CMe), 4.45 (s, 3H, NMe).

Tosylhydrazones **3**, **7**, **11**

Equimolar amounts of the respective ketone and p-toluenesulfonohydrazide in ethanol (2 ml / mmol) were refluxed for 20 min after addition of 3 N HCl (0.05 ml / mmol of **2** and **6**, and 15 ml in case of **10**). The products were collected by filtration and recrystallized from ethanol (**3**, **7**) and ethanol / water (**11**), respectively.

(*E*)-**3**: M.p. 177–179 °C (decomp.). – ^1H NMR (d_6-DMSO): δ = 2.40 (s, 3 H, CMe), 2.43 (s, 3 H, CMe), 4.05 (s, 3 H, NMe), 11.55 (br, 1 H, NH, exchangeable with D_2O) [$CDCl_3$: 9.53 / 9.12 (concentration: 10 / 5%)].

(*Z*)-**7**: M.p. 144–145 °C. – ^1H NMR (d_6-DMSO): δ = 2.33 (s, 3 H, CMe), 2.40 (s, 3 H, CMe), 4.47 (s, 3H, NMe), 11.08 (s, 1H, NH, exchangeable with D_2O) [$CDCl_3$: 11.30 (no high-field shift on dilution)].

11 · H_2O: M.p. 123–125 °C. – ^1H NMR (d_6-DMSO): δ = 2.35 (s, 3 H, Me), 2.40 (s, 3 H, Me), 11.25 (br, 1 H, NH, exchangeable with D_2O).

Hydrazones **4**, **8**, **12**

A solution of the respective ketone (10 mmol) and 85% hydrazine hydrate (for **4** and **8**: 1.25 g; for **12**: 1.77 g) in abs. ethanol (10 ml; for **4** and **8**) or ethanol (10 ml; for **12**) was heated at reflux for 30 min. In case of **8**, the product was collected after evaporation to dryness, while **4** and **12** · NH_2NH_2 were deposited from the reaction mixture on cooling. Recrystallization was effected with ethanol.

4: Yield 0.31 g (22%); m.p. 169–172 °C (decomp.). – ^{1}H NMR (d_6-DMSO): δ = 2.22 / 2.27 (2 s, 2 / 1 H, CMe), 4.13 / 4.16 (2 s, 1 / 2 H, NMe), 4.5–6.5 (br, > 2 H, NH_2, exchangeable with D_2O).

8: Yield 0.68 g (49%); m.p. 125–127 °C [18]. – ^{1}H NMR (d_6-DMSO): δ = 2.15 (s, 3 H, CMe), 4.32 (s, 3 H, NMe), 6.97 (br, 2 H, NH_2, exchangeable with D_2O).

12 · NH_2NH_2: Yield 1.43 g (91%); m.p. 137–140 °C. – ^{1}H NMR (d_6-DMSO): δ = 2.19 / 2.24 (2 s, *ca.* 1 / *ca.* 2 H, Me), 6.53 (br, *ca.* 7 H, NH_2, $NH_2NH_3^+$, exchangeable with D_2O). – For conversion of this material into the *sodium salt*, a solution of 1.34 g (8.5 mmol) and NaOH (0.37 g, 9.3 mmol) in water was evaporated to dryness; the residue was dried at 120 °C for 5 h and then treated with boiling abs. ethanol (100 ml). Filtration after cooling to room temperature gave 1.04 g (83%) of a solid; m.p. ≥ 308 °C (decomp.).

5-(1-Diazoethyl)-1 / 2-methyltetrazole (**1** / **5**)

To a light-protected suspension of **4** and **8** (0.23 g, 1.64 mmol), respectively, and activated Ag_2O (0.465 g, 2.00 mmol) in anhydrous ether (20 ml) a small quantity of pulverized NaOH was added and the mixture stirred at 10 °C for 1 h with repeated sonication. Filtration and evaporation at 20 °C afforded a residue which was recrystallized from ether (**1**) or light petroleum (30–40 °C) (**5**).

1: Yield 0.18 g (79%); pale yellow needles, m.p. 86–87 °C. – IR (KBr): $\tilde{\nu}$ = 2060, 1530 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H, CMe), 4.02 (s, 3 H, NMe).

5: Yield 0.19 g (84%); coarse orange needles, m.p. 47–49 °C. – IR (KBr): $\tilde{\nu}$ = 2060, 1520 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.28 (s, 3 H, CMe), 4.29 (s, 3 H, NMe).

5-(1-Diazoethyl)tetrazolide (*anion of* **9**)

To a solution of the sodium salt of **12** (0.044 g, 0.29 mmol) in d_6-DMSO (0.75 ml) activated Ag_2O (0.09 g, 0.39 mmol), some $MgSO_4$ and a trace of pulverized NaOH was added. The mixture was stirred for 30 min at room temperature with occasional sonication and, after removal of the solids, analyzed by NMR. – ^{1}H NMR: δ = 2.20 (s, 3 H, Me). – ^{13}C NMR: δ = 10.0 (q, Me), 45.1 (s, C=N_2), 154.1 (s, C-5). – Addition of methyl iodide (0.025 ml, 0.4 mmol): ^{1}H NMR: δ = 2.24 / 2.35 (2 s, 2.1 / 0.9 H, CMe), 4.04 / 4.36 (2 s, 0.9 / 2.1 H, NMe).

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[9] R. J. Spear, Aust. J. Chem. **37**, 2453 (1984).

[10] D. Moderhack, A. Beißner, Z. Naturforsch. **47b**, 1803 (1992).

[11] For a different reactivity of stereoisomers in the Bamford-Stevens reaction, see ref.[4] and the literature cited therein.

[12] In the case of **2** → **4**, some deacetylation was observed as side reaction (formation of 1-methyltetrazole and acetohydrazide); for this behaviour *cf.* ref.[6c] and D. Moderhack, Liebigs Ann.Chem. **758**, 29 (1972).

[13] This reaction cannot be exploited preparatively, because sensitivity of **5** towards chromatographic adsorbents vitiates separation of the isomers (see also the instability of 2-substituted 5-(diazomethyl)tetrazoles [5]).

[14] M.p. > 250 °C (decomp.); prepared from the aldehyde [D. Moderhack, Chem.-Ztg. **101**, 403 (1977)] similarly to the sodium salt of **12**, but with replacement of NaOH by $NaHCO_3$.

[15] *Cf.* ref.[2c], p. 16.

[16] All new compounds gave satisfactory C,H,N analyses (purity of **14** checked by ^{1}H NMR only).

[17] ^{1}H NMR ($CDCl_3$): δ = 2.11 (d, *J* = 8 Hz, 3 H, CH*Me*), 4.17 (s, 3 H, NMe), 5.30 (q, *J* = 8 Hz, 1 H, C*H*Me).

[18] Ref.[8] reports m.p. 173–175 °C (identity of compound however questionable in view of impure precursor to **5**).