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The synthesis of 3-diazo-2-nitromethylenepiperidine

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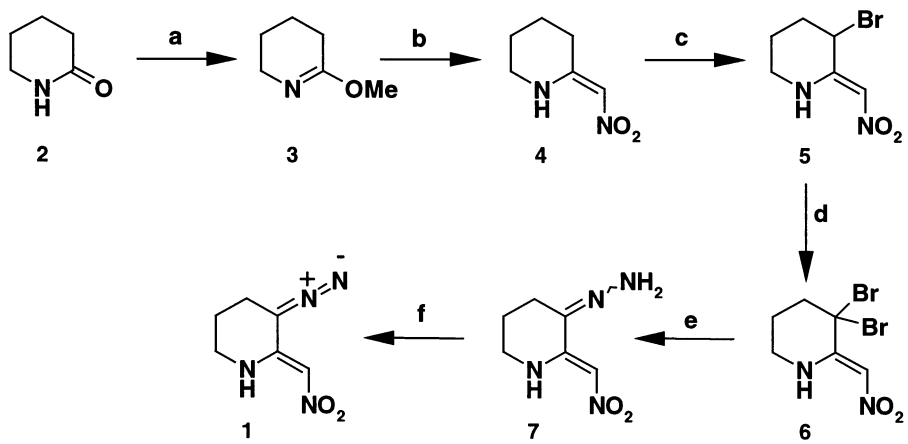
Abstract—The synthesis of 3-diazo-2-nitromethylenepiperidine, in six steps from 2-piperidone, is reported. This is the first compound described which contains the 3-diazo-1-nitropropene function. The title compound is stable enough to be isolated and characterised in gram quantities using standard organic chemistry techniques and was used to prepare some 5-aza-spiro[2.5]octane and 4,5,6,7-tetrahydro-1*H*-pyrazolo-[4,3-*b*]pyridine derivatives.

Diazo compounds are of great utility in organic synthesis. In general, the most widely used are the more stable derivatives. These are stabilised by possessing one or more electron-withdrawing groups adjacent to the diazo function. The electron-withdrawing groups most commonly encountered include ketones, carboxylic acids, esters and amides.[1] We were interested in establishing if any other electron-withdrawing functions could be used to afford stable diazo-containing compounds. We chose to investigate the nitroethylene group as it is found in a number of important bioactive molecules such as histamine H_2-antagonists[2] and nitromethylene insecticides.[3] In this paper we describe the preparation and some chemical reactions of 3-diazo-2-nitromethylenepiperidine **1**, the first reported compound to possess a diazo function stabilised by a nitroethylene group. Additionally we report the novel transformation of a dibromomethylene group to a hydrazone in one step.

The synthetic route to **1** is outlined in Scheme 1. 2-Piperidone **2** was heated in dimethyl sulphate at 55°C to afford 2-methoxy-3,4,5,6-tetrahydropyridine **3** in 88% yield. Reaction of **3** with nitromethane at 100°C for 18 h (with continual removal of the methanol produced by distillation), gave the 2-nitromethylenepiperidine **4** in 57% yield.[4] Treatment of **4** with NBS in carbon tetrachloride at reflux led to the



Scheme 1. (a) Me_2SO_4, 55°C, 20 h; (b) $MeNO_2$, 100°C, 18 h; (c) NBS, CCl_4, rt, 2 h, then reflux, 1 h; (d) NBS, CCl_4, rt, 2 h then reflux, 1 h; (e) $NH_2NH_2{\cdot}H_2O$, EtOH, rt, 20 h; (f) HgO, KOH (cat), $CHCl_3$, −5°C, 10 min.

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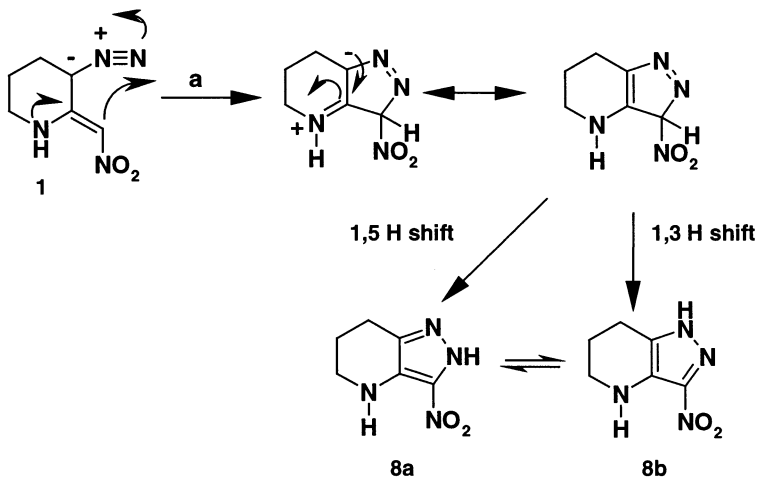
formation of 3-bromo-2-nitromethylenepiperidine **5** in 81% yield from **4**. This compound could be converted to the hydrazone **7** by treatment with four equivalents of hydrazine. However we obtained a yield of only ca. 10% which was too low to make it an attractive step in the route to our target **1**. This reaction is analogous to that reported by Hauptmann et al. for α-bromoketones.[5] The monobromo derivative **5** was subjected for a second time to the bromination protocol described above to afford 3,3-dibromo-2-nitromethylenepiperidine **6** in 71% yield. Treatment of **6** with four equivalents of hydrazine in ethanol at 25°C for 20 h led to 3-hydrazono-2-nitromethylenepiperidine **7** in 37% yield.[6] Oxidation of **7** with yellow mercuric oxide at −5°C in the presence of a catalytic amount of KOH led to the rapid formation of the 3-diazo-2-nitromethylenepiperidine **1** in 74% isolated yield.

Compound **1** was stable to purification by flash chromatography and was a yellow crystalline solid which could be stored in a freezer at −20 to −30°C for up to 6 months without significant decomposition.[6] At ambient temperature it was stable enough for all the usual analytical characterisation to be performed, to confirm its structure. In particular CI-MS afforded a molecular ion (M+1 = 169) and a characteristic M−28 peak at 141 (for loss of N_2) and the IR spectrum showed a strong absorbance at 2070 cm^{-1} for the diazo group.

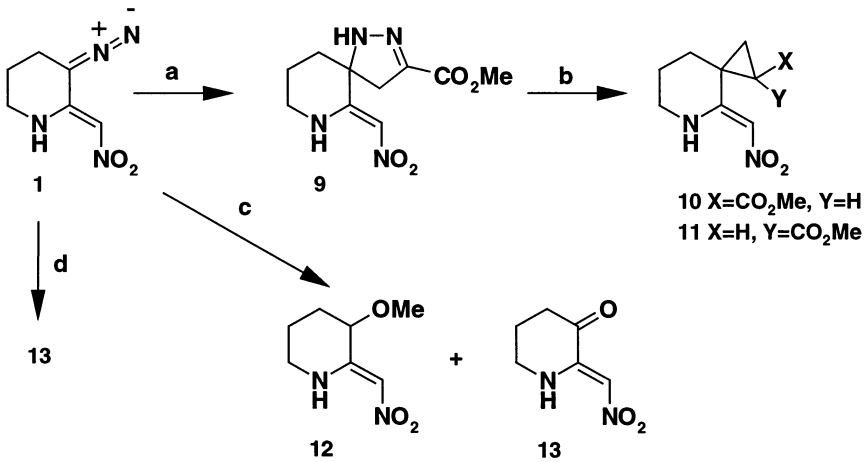
Additional proof of the structure of **1** was provided by the observation that a solution of **1** in chloroform underwent a slow rearrangement to a tautomeric mixture of the 4,5,6,7-tetrahydro-pyrazolo-[4,3-*b*]pyridine derivatives **8a** and **8b** in quantitative yield.[6] Scheme 2 outlines a possible mechanism for the rearrangement, which was complete after 36 h at 25°C. This intramolecular reaction was not unexpected as in molecule **1** the nucleophilic end of the nitroenamine function is favourably positioned to react with the electrophilic end of the diazo group. The structures of **8a** and **8b** were deduced from CI-MS which gave the same molecular ion (M+1 = 169) as for the diazo compound **1**, but no peak at 141 for loss of N_2. The IR spectrum of the **8a** and **8b** mixture had no peak for a diazo group. The ^{1}H NMR ($CDCl_3$) had no vinylic proton resonance and one N-H proton signal at δ 5.0 indicating it was not intramolecularly H bonded to the nitro group (as is observed for compounds **1** and **4**–**7** and confirmed in X-ray studies of **4** which show that the nitro group is *cis* to the ring nitrogen).[7] Additionally a very broad N-H proton was observed at δ 11.5–14.0 for the pyrazole N-H. When the ^{1}H NMR spectrum was run in DMSO-d_6 both the N-H signals became sharper and each separated into two distinct peaks. These peaks coalesced at 80°C indicating **8a** and **8b** are two compounds in equilibrium.

The isomerisation of **1** to **8a** and **8b** has not precluded the study of some of the chemistry of this new diazo derivative (Scheme 3). Thus **1** was found to undergo smooth 1,3-dipolar addition to methyl acrylate to afford the spirocyclic pyrazoline **9** in 60% yield. This pyrazoline was found to extrude nitrogen when heated in 1,2-dichlorobenzene at 180°C for 15 min to give a 3:1 mixture of the 5-aza-spiro[2.5]octane derivatives **10** and **11** in a combined yield of ca. 65% which were separable by silica gel chromatography.[6] The 5-aza-spiro[2.5]octane system has received limited attention in the literature to date, with only a few simple derivatives having been described in some recent patents.[8]

Carbene insertion reactions have only been briefly explored so far. Thus rhodium(II) acetate decomposition of **1** in methanol leads to the expected insertion product **12** albeit in only 15% yield.[9] A major side product in this reaction was found to be the ketone **13**. The mechanism of formation of this ketone has yet to be established. However, when **1** was decomposed in a variety of solvents which could act as oxygen donors (e.g. DMSO, acetone, nitrobenzene) the ketone derivative **13** was the main product isolated in yields ranging from 54 to 70%. The reaction of **1** with ethyl vinyl ether in the presence of rhodium(II) acetate failed to give the expected cyclopropyl product but yielded only ketone **13** in ca. 30% yield.



Scheme 2. (a) $CHCl_3$, rt, 36 h.



Scheme 3. (a) Methyl acrylate, 25°C, 5 h; (b) 1,2-dichlorobenzene, 180°C, 15 min; (c) Rh(II) acetate, MeOH, rt, 30 min; (d) Rh(II) acetate, DMSO, rt, 30 min.

Further details of these and other chemical reactions of this novel class of diazo derivative will be described in future papers.

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References

1. (a) Doyle, M. P.; Anthony, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropane to Ylides*; John Wiley and Sons: New York, 1998; (b) Zollinger, H. *Diazo Chemistry II. Aliphatic, Inorganic and Organometallic Compounds*; VCH: Weinheim, Germany, 1995.
2. Bays, D. E.; Stables, R. In *Annual Reports in Medicinal Chemistry*; Hess, H.-J., Ed.; Academic: New York, 1983; Vol. 18, p. 89.
3. (a) Soloway, S. B.; Henry, A. C.; Kollmeyer, W. D.; Padgett, W. M.; Powell, J. E.; Roman, S. A.; Tieman, C. H.; Corey, R. A.; Horne, C. A. In *Advances in Pesticide Sciences*; Geissbuhler, H.; Brooks, G. T.; Kerney, P. G., Eds.; Pergamon: Oxford, 1979; Vol. 2, p. 206; (b) Buckingham, S. D.; Balk, M. L.; Lummis, S. C. R.; Jewess, P.; Satelle, D. B. *Neuropharmacology* **1995**, *34*, 591.
4. (a) Jones, K.; Newton, R. F.; Yarnold, C. J. *Tetrahedron* **1996**, *52*, 4133; (b) Payne, G. B. US Patent No. 4,025,634, 1977; *Chem. Abstr.* **1977**, *85*, 167885a.
5. Hauptmann, S.; Klugo, M.; Seidig, K.-D.; Wilde, H. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 688.
6. All compounds described have been fully characterised with IR, MS and NMR spectroscopy, elemental analysis and mp. Compound **7**: yellow solid; mp 153–156°C; IR (Nujol) ν_{max} 3178, 1658, 1601, 1485, 1383, 1347, 1233, 1186, 1144, 884, 767 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 10.6 (1H, bs), 7.95 (2H, bs), 7.0 (1H, s), 3.35 (2H, m), 2.3 (2H, t, $J=6.9$ Hz), 1.7–1.8 (2H, m); ^{13}C NMR (DMSO-d_6, 60 MHz) δ 154, 130, 103, 40, 21, 19; CIMS m/z 171(M+1); anal. found: C, 42.2; H 5.9; N, 32.2% calcd for $C_6H_{10}N_4O_2$: C, 42.4; H, 5.9; N, 32.9%. Compound **1**: orange-red solid; mp 105–107°C; IR ($CHCl_3$) ν_{max} 3200, 3140, 2070, 1580, 1390, 1365, 1166, 1094, 970, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.4 (1H, bs), 6.6 (1H, s), 3.4 (2H, m), 2.75 (2H, t, $J=6.3$ Hz), 2.0 (2H, m); CIMS (NH_3) m/z 186 (M+18), 169 (M+1), 158, 141 (M–28); anal. found: C, 42.98; H, 4.79; N, 32.95% calcd for $C_6H_8N_4O_2$: C, 42.86; H, 4.76; N, 33.33%. Compound **8** (mixture of **8a** and **8b**): red solid; mp 142–146°C; IR (Nujol) ν_{max} 3182, 3095, 1609, 1495, 1456, 1375, 1337, 1321, 1230, 1186; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.5–14.0 (1H, bs), 4.8–5.2 (1H, bs), 3.38 (2H, t, $J=5.5$ Hz), 2.9 (2H, t, $J=6.4$ Hz), 2.0 (2H, m); CIMS m/z 169 (M+1), 153, 137, 121; anal. found: C, 42.99; H, 4.85; N, 33.52% calcd for $C_6H_8N_4O_2$: C, 42.86; H, 4.76; N, 33.33%. Compound **9**: yellow solid; mp 178–180°C; IR (Nujol) ν_{max} 3332, 3155, 1720, 1607, 1567, 1455, 1310, 1242, 1192, 1099, 976 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 10.5 (1H, bs), 8.75 (1H, bs), 6.4 (1H, s), 3.6 (3H, s), 3.3 (2H, m), 3.05 (1H, d, $J=16.5$ Hz), 3.0 (1H, d, $J=16.5$ Hz), 1.7–1.9 (4H, m); ^{13}C NMR (DMSO-d_6, 60 MHz) δ 163, 162, 136, 107, 66, 52, 45, 41, 30, 18; CIMS m/z 255 (M+1), 227 (M–28); anal. found: C, 47.5; H 5.6; N, 22.0% calcd for $C_{10}H_{14}N_4O_4$: C, 47.25; H, 5.5; N, 22.0%. Compound **10**: pale yellow solid; mp 140–142°C; IR (Nujol) ν_{max} 3274, 3141, 1713, 1592, 1435, 1321, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.9 (1H, bs), 6.2 (1H, s), 3.63 (3H, s), 3.5 (2H, m), 2.1 (1H, dd, $J=7$, 8.6 Hz), 1.7–1.9 (4H, m), 1.5 (1H, dd, $J=5.92$, 8.6 Hz), 1.45 (1H, t, $J=7$ Hz); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 170, 163, 105, 52, 41, 30, 26, 24, 21, 20; CIMS m/z 227 (M+1); anal. found: C, 52.9; H 6.2; N, 12.4% calcd for $C_{10}H_{14}N_2O_4$: C, 53.1; H, 6.2; N, 12.4%. Compound **11**: off-white solid; mp 148–149°C; IR (Nujol) ν_{max} 3270, 3143, 1720, 1591, 1345, 1245, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.3 (1H, bs), 6.5 (1H, s), 3.6 (3H, s), 3.5 (2H, m), 1.95–2.1 (3H, m), 1.95 (1H, dd, $J=6.2$, 8.1), 1.75 (1H, t, $J=6.2$), 1.27 (1H, m), 1.20 (1H, dd, $J=6.2$, 8.1); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 169, 158, 110, 52, 40, 31, 30, 28, 21, 16; CIMS m/z

227 (M+1); anal. found: C, 53.0; H 6.2; N, 12.4% calcd for $C_{10}H_{14}N_2O_4$: C, 53.1; H, 6.2; N, 12.4%.
7. BeBoer, J. J.; Bright, D. *Acta Crystallogr.* **1975**, *B31*, 2342–2344.
8. (a) Kim, W. J.; Park, M. H.; Ha, J. D.; Baik, K. U. EP Patent No. 550025, 1993; *Chem. Abstr.* **1993**, *119*, 225838; (b) Yang, B. V. WO Patent No. 9222550, 1992; *Chem. Abstr.* **1993**, *123*, 233896; (c) Kin, K.; Kawa, Z.; Haku, K. JP Patent No. 07300460, 1995; *Chem. Abstr.* **1996**, *124*, 202006.
9. Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.