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SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3673–3675

Direct ring functionalisation of 1,4,7-trimethyl-1,4,7-triazacyclononane and its application in the preparation of functional $[L_2Mn_2O_3]$-type complexes

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Received 1 February 2006; revised 10 March 2006; accepted 22 March 2006
Available online 12 April 2006

Abstract—Treatment of 1,4,7-trimethyl-1,4,7-triazacyclononane (metacn) with *N*-bromosuccinimide (NBS) gave a bicyclic ammonium intermediate, which was ring-opened to 2-cyano-1,4,7-trimethyl-1,4,7-triazacyclononane by reaction with potassium cyanide. Reduction to the amine followed by reaction with anhydrides gave amides, which could subsequently be converted to dinuclear tris-μ-oxo manganese complexes.

The ligand 1,4,7-trimethyl-1,4,7-triazacyclononane (metacn) and derivatives are reported to give numerous transition metal complexes.[1] In particular, the catalytically active dinuclear manganese tris-μ-oxo-metacn $[L_2Mn_2O_3]^{2+}$ complex has been the subject of many studies,[2] for example, the bleach activity of hydrogen peroxide in laundry formulations could be boosted,[2a] the epoxidation of olefins with hydrogen peroxide in water[2b] or organic solvents[2c] and other catalytic oxidation processes.[2d–f] The coordination behaviour and catalytic activity has also generated interest in homologues and derivatives to tune the behaviour of the resulting complexes. Substitution on the nitrogens is straightforward starting from the 1,4,7-triazacyclononane (tacn) intermediate.[3] However, substitution on carbons of the nine-membered ring with functional groups requires total synthesis for each derivative. Also the harsh ring-forming conditions might prohibit introduction of most functional groups.[4,5] In this letter, we report for the first time a new method for functionalisation of a triazacycle ring carbon starting from the readily accessible metacn allowing the introduction of functional groups such as an amine or a carboxylic acid. Conversion to the corresponding $[L_2Mn_2O_3]^{2+}$ complex is also demonstrated which can be further derivatised.

Direct functionalisation of amines at their α-position has been described in the literature.[6] However, simple amines are discussed and extension of this chemistry to the metacn ligand may not be straightforward. Initially, the oxidation of tertiary amines using mercury acetate,[7] potassium hexacyanoferrate(III)[8] and by electrochemistry[9] was investigated. An iminium intermediate might be generated, which could subsequently be reacted with a nucleophile. *N*-Bromosuccinimde (NBS) was used as an oxidant as this should lead to a similar oxidation[10] product, which might precipitate as the iminium bromide, thereby stopping the reaction after oxidation at one of the three amine groups.

Treatment of metacn with NBS in tetrahydrofuran (THF) gave an exothermic reaction and a precipitate was observed. The hygroscopic solid was proved by NMR and mass spectrometry to consist of a mixture of the HBr salts of the iminium product and metacn. When solid anhydrous potassium carbonate was added together with NBS to the reaction mixture, metacn. HBr was no longer observed in the precipitate. The precipitate was stirred with acetonitrile to dissolve the iminium product and the inorganic salts were removed by filtration. The reaction could be carried out on a 0.1–0.2 mol scale.[11]

Keywords: N-ligands; Manganese; Macrocyclic ligands; Amines; Oxidation; Synthetic methods.
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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.134

The structure of the precipitated product as derived from NMR and mass spectroscopy is shown in Figure 1. The bicyclic structure is the result of an internal nucleophilic attack on the iminium carbon. Reaction of iminium ions with cyanide is known[12] and although no iminium function is present in the bicyclic molecule, we attempted the reaction. Addition of cyanide opened the bicyclic structure to form a nine-membered ring. The resulting product contained a variable but small amount of metacn, which could be easily removed by vacuum distillation. According to NMR the distilled product was >95% pure and had the expected structure.[11] Scheme 1 shows the reduction of the nitrile group to the corresponding aminomethyl group with lithium aluminium hydride in refluxing THF.[13] After work-up the product, **L1** was purified by vacuum distillation and obtained in 25% yield based on metacn over three steps.[14]

In order to form an Mn_2O_3 complex, the primary amino group needed to be protected as during complexation the protected amino group is less prone to participate in coordination. Acylation of the primary amine was accomplished using acetic anhydride or Boc-anhydride giving the corresponding amides **L2** or **L3**.[15] The Boc group is widely used for protection of amines and it was expected that it could be removed by milder acid treatment[16] than the acetyl group. Also, the Mn complex was expected to be stable towards acid treatment. Both ligands **L2** and **L3** could indeed be converted in the usual way into coordination complexes.[2c,17] Acid treatment of the Boc-complex followed by purification showed that deprotection occurred but was incomplete and the deprotected complex could not be isolated in pure form. Optimisation of the Boc cleavage, purification and the coupling possibilities of the deprotected amino group (e.g., via EDDS to Boc-protected glycine as shown in the Supplementary data) need further investigation.

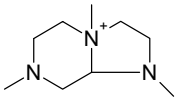
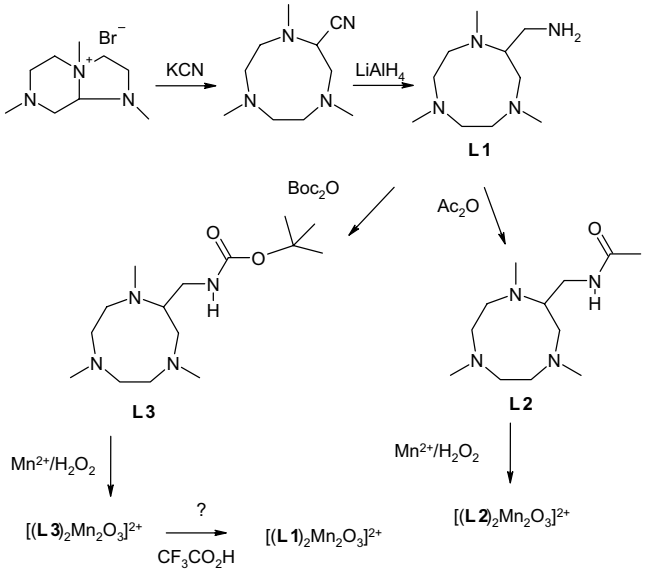


Figure 1. The structure of the NBS oxidation product of metacn.



Scheme 1. Reactivity of the oxidation product and conversion to the amide manganese complexes.

Acknowledgements

Dr. S. B. Tjan and J. Niël are gratefully acknowledged for recording the NMR spectra. Dr. P. J. W. Schuyl, C. J. Platerink, J. J. Schilt and T. de Joode recorded the mass spectra and helped with their interpretation. At the URUS-Edgewater laboratories (USA), L. Hargiss recorded the mass spectra of some of the ligands and complexes and Victor DeFlorio helped with GLC analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.134.

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11. Oxidation of 1,4,7-Me_3TACN and reaction with cyanide. To a mixture of dry potassium carbonate (12 g) and 1,4,7-Me_3TACN (0.1 mol, 17.1 g) dissolved in dry tetrahydrofuran (THF, 100 ml) was added a solution of *N*-bromosuccinimide (NBS, 0.1 mol 17.8 g) in THF (300 ml) dropwise while stirring over a 2 h period at 50 °C under argon. The resulting precipitate was isolated and subsequently washed with THF and then redissolved in acetonitrile. Evaporation of an aliquot and analysis demonstrated the presence of the bicyclic intermediate. ^{1}H NMR (360 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.42 (s, 3H), 2.6–2.95 (m, 6H), 3.27 (s, 3H), 3.55 (m, 2H), 3.6–3.9 (m, 3H); ^{13}C NMR (90.5 MHz, DMSO-d_6): δ 37.1, 44.5, 48.0, 48.1, 48.7, 51.2, 57.5, 60.7, 85.3; FAB-Ms. (matrix: nitrobenzyl alcohol) positive mode: *m*/*z* 170.2 (M+), 172 (trace of 1,4,7-Me_3TACN+H), 421.2 (M+Br+M). MSMS of 170: *m*/*z* 170, 127, 113, 84, 82, 70, 58, 44, 42, negative mode: *m*/*z* 153, 151 (Br+NBA), 81, 79 (Br). To the acetonitrile solution was added while stirring, potassium cyanide (0.15 mol, 10 g) and water (25 ml) at ambient temperature. The resulting cyanide was isolated by evaporation, redissolved in dichloromethane, dried over anhydrous sodium sulfate, filtered and evaporated. The crude oil obtained, which contained a small amount of metacn, was purified by vacuum distillation (7.8 g, 0.04 mol, 40%) ^{1}H NMR (360 MHz, $CDCl_3$): δ 2.40 (m, 1H), 2.39 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 2.5–2.9 (m, 7H), 3.12 (m, 1H), 3.42 (dd, *J* 9.5 Hz, 14.4 Hz, 1H), 3.88 (dd, *J* 3.1 Hz, 9.5 Hz, 1H). The multiplets between 2.5 and 2.9 ppm were too complex to resolve. ^{13}C NMR (90.5 MHz, $CDCl_3$): δ 44.4, 46.2, 46.8, 52.7, 56.3, 56.8, 57.1, 57.3 (×2), 117.6; GC/MS (CI, NH_3): at 7.37′ *m*/*z* 169 (degradation product probably obtained by release of HCN at the injection gate of the GC apparatus) and at 10.05′ *m*/*z* 196 (product); IR (NaCl): *v* (cm^{-1}) 2920, 2840, 2780, 2210, 1450, 1360, 1310, 1100, 1070, 1025, 970, 890.
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14. 2-(Aminomethyl)-1,4,7-Me_3TACN (**L1**). Reduction of 2-cyano-1,4,7-Me_3TACN (25 mmol, 4.9 g) with lithium aluminium hydride (25 mmol, 0.95 g) in dry THF (100 ml) in the usual way[12] and purification by vacuum distillation at 92 °C (0.05 mmHg) gave a clear oil (3.2 g, 64%) which rapidly turned yellow upon exposure to air. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.2 (br s, 2H), 2.35 (s, 9H), 2.2–2.8 (m, 12H), 3.18 (m, ^{1}H); ^{13}C NMR (90.5 MHz, $CDCl_3$): δ 36.5, 41.8, 47.0, 47.1, 55.2, 56.2, 56.5, 58.4, 58.6, 64.0; GC/MS: *m*/*z* 201 (M+1); IR (NaCl): *v* (cm^{-1}) 3368, 2960, 1590, 1450, 1370, 1210, 1110.
15. 2-(Acetamidomethyl)-1,4,7-Me_3TACN (**L2**) and 2-(*N*-Boc-amidomethyl)-1,4,7-Me_3TACN (**L3**). Treatment of a solution of **L1** in chloroform with either acetic anhydride or Boc anhydride in chloroform and 1 equiv of triethylamine at 40 °C for 15 min resulted after work-up washing drying and evaporation, in the amides **L2** and **L3**. Data for **L2** ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.29 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 2.4–2.8 (m, 10H), 3.5 (m, 3H), 6.4 (br s, 1H); ^{13}C NMR (90.5 MHz, $CDCl_3$): δ 23.3, 35.8, 39.1, 47.0, 47.1, 54.9, 56.2, 56.9, 58.6, 58.9 (×2), 170.0. IR (NaCl) *v* (cm^{-1}): 3400, 1630, 1560. Data for **L3** ^{1}H NMR (360 MHz, $CDCl_3$): δ 4.95 (br s, 1H), 3.41 (m, 1H), 3.23 (m, 1H), 3.06 (m, 1H), 2.9–2.5 (m, 10H), 2.3 (3 × s, 9H), 1.42 (s, 9H); ^{13}C NMR (90.5 MHz, $CDCl_3$): δ 28.4 (3 × CH_3), 36.3, 40.2, 47.1, 47.2, 54.6, 56.0, 56.3, 58.2, 58.3, 59.8, 160.4 (some signals overlap). IR (NaCl): *v* (cm^{-1}) 3380, 2960, 1716, 1487, 1455, 1364, 1170.
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17. [**L2**$_2$$Mn_2O_3$]$(PF_6)_2$ and [**L3**$_2$$Mn_2O_3$]$(PF_6)_2$ were prepared according to the procedures described previously.[3c,4b] **L2** and **L3** were converted to the crude manganese(IV) complexes. Column chromatography on silica (eluent acetonitrile with 10 mmol/l KPF_6) gave the complexes as a red glass. [**L2**$_2$$Mn_2$O3]$(PF_6)_2$ UV–vis (acetonitrile): λ_{max} (ε: l mol^{-1} cm^{-1}) 492 nm (100), 395 nm (500), 315 nm (6000), 276 nm (9300), 239 nm (9700); mass spectrometry ESP(+) (methanol/water): +*m*/*z* 787 [**L2**$_2$$Mn_2O_3$]$(PF_6)$+, 321 [**L2**$_2$$Mn_2O_3$]$^{2+}$, 243 (**L2**+H)$^+$ and unassigned signals at 816, 335.5 (816-PF_6)/2, 356, 197. [**L3**$_2$$Mn_2O_3$]$(PF_6)_2$ UV–vis (CH_3CN): λ_{max} (ε l mol^{-1} cm^{-1}) 234 nm (9400), 279 nm (9200), 314 nm (8060), 390 nm (sh, 1200), 487 nm (350); IR (KBr) *v* (cm^{-1}): 3646, 3434, 2980, 1703, 1573, 1520, 1462, 1166, 840, 663; Mass spectrometry ESP(+) (acetonitrile/water 1:1) *m*/*z*: 903.30 [**L3**$_2$$Mn_2O_3$]$(PF_6)^+$.