A New Methodology for the Reductive Cyclization of ω-Azido Carbonyl Compounds Mediated by Tetrathiomolybdate: Application to an Efficient Synthesis of Pyrrolo[2,1-c][1,4]benzodiazepines

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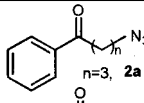
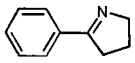
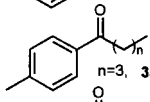
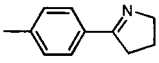
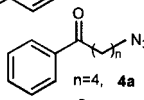
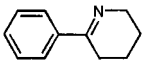
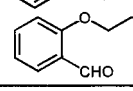
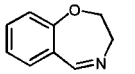
Abstract: The ω-azido carbonyl compounds on treatment with tetrathiomolybdate, **1** led to the formation of 5, 6 and 7 membered cyclic imines in very good yields under mild conditions. This method is applied successfully to a new efficient synthesis of 1,4-benzodiazapinone derivatives and in particular Bzl DC-81.

There is presently considerable interest in DNA-binding ligands such as pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) as potential antitumour agents and gene targetted drugs.[1] The PBD class of antitumour antibiotics are produced biosynthetically by various *streptomyces* species. Their antitumour activity is due to covalent binding in the minor groove of DNA through nucleophillic attack of the N-2 of a guanine base on the electrophilic C-11 position of the PBD. This aminal linkage thus interfaces with DNA function .[2] Hence the synthesis of this kind of cyclic imine has attracted considerable attention in the past few years.[3] Various approaches to the synthesis of these imines have been investigated with varying degrees of success and limitations. The most promising of these approaches is the aza-Wittig reaction of ω-azidocarbonyl compounds with triphenylphosphine.[4] In this communication we report a new approach to a facile synthesis of 5,6 and 7 membered cyclic imines from the corresponding ω-azido carbonyl compounds mediated by benzyltriethyl-ammonium tetrathiomolybdate, $[PhCH_2NEt_3]_2MoS_4$, (**1**) and its application to an efficient synthesis of pyrrolo[2,1-c] [1,4]benzodiazepines in general and Bzl DC-81 (**8b**) in particular.

Earlier we had shown that tetrathiomolybdate **1** is a useful reagent for the reductive dimerization of organic thiocyanates and selenocyanates to the corresponding disulfides[5] and diselenides[6] and also for the reduction of aryl azides to arylamines.[7] Therefore it was of interest to study the reaction of tetrathiomolybdate **1** with ω-azidocarbonyl compounds and the results are summarized in Table 1.

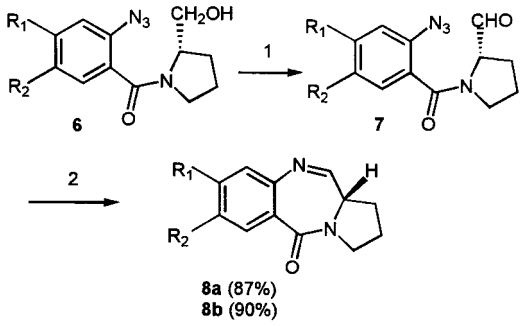
Table 1

Entry	Substrates	Time (h)	Product	Yield [a,b]
1	 n=3, **2a**	16	 **2b**	81[10]
2	 n=3, **3a**	12	 **3b**	79[10]
3	 n=4, **4a**	10	 **4b**	82[10]
4	 **5a**	16	 **5b**	67[11]

a. Yield refers to isolated, pure products, b. All the products exhibited expected spectral and analytical data

When azido ketones **2a**, **3a**, and **4a** were treated with tetrathiomolybdate **1** (1 equiv.) in CH_3CN (25°C, 10-16 h) the 5 and 6 membered cyclic imines **2b**, **3b** and **4b** respectively were formed in very good yields. Similarly the azido aldehyde **5a** underwent a smooth reductive cyclization with **1** to form the seven membered cyclic imine **5b** (67%).

This methodology was then extended to a successful synthesis of pyrrolo[2,1-c][1,4]benzodiazepines **8a** and Bzl DC-81, **8b**. The precursors for **8a** and **8b** were prepared by Swern oxidation of the corresponding alcohols **6a** and **6b**[8] to give (2S)-N-(2-azidobenzoyl)pyrrolidine-carboxaldehydes **7a** and **7b**[8] respectively. Further reaction of these azido aldehydes **7a** and **7b** with tetrathiomolybdate **1** at room temparature led to the PBD imines **8a** and **8b** respectively in very good yields (87% and 90% respectively) (Scheme) .



a: R_1=R_2=H ; b: R_1= -OBn, R_2= -OMe
1) DMSO, $(COCl)_2$, Et_3N. 2) $[PhCH_2NEt_3]_2MoS_4$, CH_3CN, 10h, RT.

Scheme

In summary we have shown the efficacy of a general method for the reductive cyclization of ω-azido carbonyl compounds with tetrathiomolybdate **1** and its application to the synthesis of DNA interactive PBDs in their imine form under mild and neutral conditions.

Typical experimental procedure:

8-Benzyl DC-81, 8b: To a well stirred solution of **7b** (0.075 g, 2mmol) in CH_3CN (3ml) was added tetrathiomolybdate **1**[9] (0.143 g, 0.24 mmol) under argon atmosphere and the mixture was stirred for 10 h at room temperature (25°C). The solvent was evaporated under vacuum and the black residue was extracted with CH_2Cl_2 : ether (1:9 , 20ml x 6). The combined extract was filtered through a Celite pad and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (eluted with 9:1 , EtOAc/ hexane) to afford 8-benzyl DC- 81, **8b** as a yellow oil (0.060 g, 90%).

$[\alpha]_D^{20}$ = +611, (c = 0.0108, $CHCl_3$) [lit.[4] $[\alpha]_D^{23}$ = +629.6 (c = 0.0108, $CHCl_3$)] ; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.65 (d, 1H), 7.54 (s 1H) , 7.48-7.31 (m, 5 H) , 6.85 (s, 1H), 5.20 (d, J= 2.8 Hz, 2H), 3.97 (s, 3H), 3.90-3.51 (m, 3H), 2.37- 1.96 (m, 4H).; IR, (neat) 3339, 2932, 2870, 1700, 1626, 1601, 1504, 1454, 1431, 1381, 1261, 1217, 1200, 1178, 1124, 1091, 1022, 755,735, 698 cm^{-1}; MS m/z 337 (M^++1), 336 (M^+), 245, 217, 91

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