Notes

Reaction of Azides with Tetrathiomolybdate: Reduction and Imine Formation

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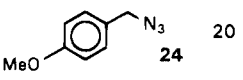
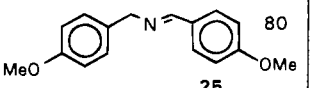
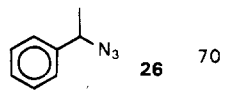
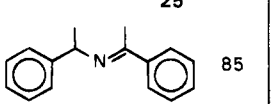
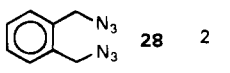
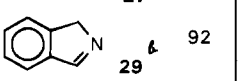
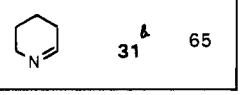
The reduction of azides to primary amines is an important transformation used extensively in organic synthesis.[1] Some recent applications include the synthesis of nitrogen-containing heterocyles[2] and carbohydrate derivatives.[3] Of the number of methods available for the conversion of azides to amines,[4] the most promising involve catalytic hydrogenation,[5] the use of triphenylphosphine–water,[6] hydrogen sulfide–pyridine–water,[7] and thiols under basic conditions.[8] Reduction of azides also has biological implications. Many molybdenum-containing enzymes are known to reduce azides to the corresponding amines.[9] In these cases it is postulated that the sulfur-ligated molybdenum is responsible for the reduction. We earlier reported that benzyltriethylammonium tetrathiomolybdate, $(PhCH_2NEt_3)_2MoS_4$ (**1**) is a good sulfur transfer reagent and that it reacts with a variety of organic substrates such as alkyl halides to produce the corresponding disulfides in good yields.[10] In continuation of our work in this area we studied the reaction of azides with tetrathiomolybdate **1**. The results of this study are presented here.

Treatment of aryl azides **2**, **4**, and **6** with 0.5 mol equiv of tetrathiomolybdate **1** in acetonitrile–water (20:1 v/v) at room temperature (25 °C) for 4–6 h gave the corresponding amines **3**, **5**, and **7** as the only products[11] in high yields (Table 1). The reaction of sulfonyl azides **8**, **10**, and **12** with **1** under the same conditions was extremely facile (0.1 h), and the sulfonamides **9**, **11**, and **13**, respectively, were the exclusive products formed in excellent yields. Similarly, acyl azides **14**, **16**, **18**, and **20** also reacted readily with tetrathiomolybdate **1** to afford the corresponding amides **15**, **17**, **19**, and **21** as the sole products. The chemoselective reduction of acyl azides **18** and **20** bearing readily reducible functional groups like nitro and aldehyde clearly illustrates the superiority of this methodology to the existing methods.[4-8] It is clear from these reactions that tetrathiomolybdate has induced a process of reduction rather than a sulfur transfer reaction.

Interestingly, when the same reaction of tetrathiomolybdate **1** was extended to alkyl azides, the reaction took a different course. Treatment of alkyl azides with **1** under the above conditions gave imines exclusively rather than the corresponding primary amines (Table 1). Thus, the reaction of primary azides **22** and **24** with **1**

Table 1. Reaction of Azides with Tetrathiomolybdate 1

Substrate	Time(h)	Product	Yield(%)
PhN_3 **2**	6	$PhNH_2$ **3**	75
p-MeCO-$C_6H_4N_3$ **4**	4	p-MeCO-$C_6H_4NH_2$ **5**	90
p-MeO_2C-$C_6H_4N_3$ **6**	4	p-MeO_2C-$C_6H_4NH_2$ **7**	92
$CH_3SO_2N_3$ **8**	0.1	$CH_3SO_2NH_2$ **9**	95
p-Me-$C_6H_4SO_2N_3$ **10**	0.1	p-Me-$C_6H_4SO_2NH_2$ **11**	96
$C_{10}H_{15}SO_2$-N_3 **12** [a]	0.1	$C_{10}H_{15}SO_2NH_2$ **13**	96
$PhCON_3$ **14**	0.5	$PhCONH_2$ **15**	90
$CH_3(CH_2)_{14}CON_3$ **16**	1	$CH_3(CH_2)_{14}CONH_2$ **17**	92
p-O_2N-$C_6H_4CON_3$ **18**	1.5	p-O_2N-$C_6H_4CONH_2$ **19**	95
p-OHC-$C_6H_4CON_3$ **20**	3	p-OHC-$C_6H_4CONH_2$ **21**	88
$PhCH_2N_3$ **22**	3	$PhCH_2N=CHPh$ **23**	82
 **24**	20	 **25**	80
 **26**	70	 **27**	85
 **28**	2	 **29** [b]	92
N_3-$(CH_2)_5$-N_3 **30**	8	 **31** [b]	65

[a] Camphor sulfonyl. [b] The crude products were reduced with $NaCNBH_3$ and were characterized as the corresponding secondary amines.

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(11) Quantitative evolution of nitrogen (identified by mass spectrometry) was noted.

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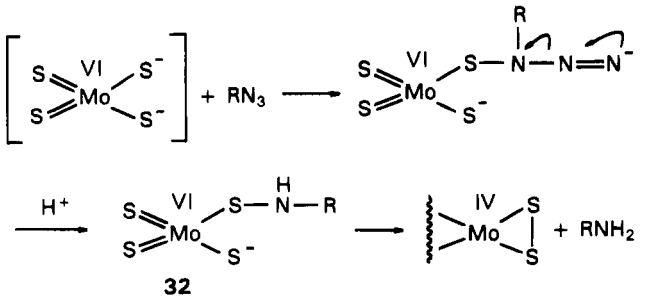
Scheme 1



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yielded the imines **23** and **25** in high yields while secondary azide **26** reacted with **1** slowly (70 h) to give the imine **27** in good yield. In order to explore the utility of this reaction for intramolecular processes, diazides **28** and **30** were treated with **1**. Indeed, cyclic imine formation took place giving **29** and **31** in very good yields.

The reduction of aryl azides to aryl amines by tetrathiomolybdate **1** is surprising since molybdenum is in the highest oxidation state (VI) and there has been no sulfur transfer to the organic substrate. However, induced internal redox processes have been reported with tetrathiomolybdate **1** where reduced molybdenum complexes have been prepared in the presence of electron acceptors.[12] Thus in the conversion of $MoS_4^{2-} \rightarrow Mo_2S_8^{2-}$ in the presence of PhSSPh it has been shown that four S^{2-} ligands are transformed to two S_2^{2-} ligands, a process which delivers four electrons. Two of the electrons are available to reduce each molybdenum by one electron, and the other two electrons are delivered to the external oxidant.[13] In the reaction of azides with **1**, it is likely that MoS_4^{2-} attacks the α-nitrogen of the azide to produce the *N*-sulfenyl amine **32** following nitrogen extrusion. This intermediate can then undergo induced internal electron transfer from S_2^{2-} to Mo(VI)[14] resulting in the cleavage of the sulfur–nitrogen bond to form the amine (Scheme 1). In the case of alkyl azides the reaction takes a different course to form the imines which is not fully understood. The difference in reactivity of alkyl azides may be due to the fact that alkylamine is a poorer leaving group than aniline, amide, or sulfonamide at neutral pH.

The reaction of aryl azides with tetrathiomolybdate **1** offers a simple, mild, and efficient methodology for the formation of the corresponding aryl amines. The reaction of alkyl azides mediated by tetrathiomolybdate **1** to form the imine derivatives is novel and may find wide application in organic synthesis.

Experimental Section

^1H and ^{13}C NMR spectra were generally recorded in $CDCl_3$. TLC were performed on 0.25 mm precoated silica plates (60F-254). The mp and bp's reported are uncorrected. Benzyltriethylammonium tetrathiomolybdate was prepared as described earlier.[10a] Azides were prepared according to the literature procedures.[1] Aqueous acetonitrile (CH_3CN:H_2O, v/v, 20:1) was used as the solvent for the reactions unless otherwise specified. Solid products were found to have sharp melting points and were pure by ^1H NMR; liquid products were purified using Kugelrohr distillation.

Representative Procedure for the Reaction of Aryl, Acyl, and Sulfonyl Azides. Reaction of azide **20** with **1**. A solution of azide **20** (0.35 g, 2 mmol) in CH_3CN (2 mL) was added to a solution of **1** (0.67 g, 1.1 mmol) in aqueous acetonitrile (10 mL) over a period of 2 min, at room temperature (25 °C). After stirring the reaction mixture for 3 h, CH_3CN was removed under reduced pressure and the residue was repeatedly extracted with ether (6 × 25 mL). The solvent was removed to obtain a yellow solid which was decolorized with charcoal and recrystallized from dilute EtOH to collect amide **21** as colorless needles (0.262 g, 88%): mp 75 °C, lit.[15] 75–76 °C; IR (nujol) 3360, 3140, 2900, 1680, 1650, 1450, 1360, 1230, 710 cm^{-1}; ^1H NMR (90 MHz, acetone-d_6) δ 10.12 (s, 1H), 8.1 (d, J = 12.8 Hz, 2H), 8.02 (d, J = 12.8 Hz, 2H), 7.7 (br s, 2H).

Representative Procedure for the Reaction of Alkyl Azides. Reaction of azide **24** with **1**. A solution of azide **24** (0.326 g, 2 mmol) in CH_3CN (2 mL) was added to a solution of **1** (0.67 g, 1.1 mmol) in aqueous CH_3CN (10 mL) all at once. After stirring the reaction mixture for 20 h, CH_3CN was removed under reduced pressure, and the residue was repeatedly extracted with ether (8 × 15 mL), concentrated, and distilled using Kugelrohr to afford imine **25**[16] as a colorless oil (0.408 g, 80%): bp 178 °C/0.5 torr, lit.[16] 178–180 °C/0.5 torr; IR (neat) 2830, 2910, 1510, 1245, 1035, 810 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$ δ 8.28 (s, 1H), 7.7 (m, 2H), 7.2 (m, 2H), 7.85 (m, 4H), 4.72 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.6, 160.9, 158.6, 135.2, 131.6, 129.8, 128.3, 113.9, 64.4, 55.1; MS (m/z) 255 (M^+), 240, 147, 122, 91, 77.

Reaction of Diazide 28 with 1. A solution of diazide **28** (0.19 g, 1 mmol) in CH_3CN (1 mL) was added to a solution of **1** (0.67 g, 1.1 mmol) in aqueous CH_3CN (10 mL) over a period of 3 min. After stirring the reaction mixture for 2 h, CH_3CN was removed under reduced pressure and the residue was extracted as described earlier to give **29** as an oil (0.11 g, 92%). The unstable crude product was immediately treated with $NaCNBH_3$ (0.06 g, 1 mmol) in methanol (5 mL) at 25 °C. After stirring the reaction mixture for 3 h, methanol was removed under reduced pressure and the residue was treated with 10% KOH solution (5 mL) for 15 min and extracted with CH_2Cl_2 (5 × 5 mL). The organic extract was dried over anhydrous Na_2SO_4, and the solvent was evaporated to afford 1,3-dihydroisoindole as a solid (0.09 g, 80%): mp 54–56 °C, lit.[17] 55–56 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 7.00 (s, 4H), 3.93 (s, 4H), 2.24 (br s, 1H).

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Supporting Information Available: Characterization data and references for **5**, **7**, **13**, **17**, **19**, **23**, and **27** and an NMR spectrum and HPLC chromatogram of **25** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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