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Molybdenum pentachloride ($MoCl_5$) or molybdenum dichloride dioxide (MoO_2Cl_2): advanced catalysts for thioacetalization of heterocyclic, aromatic and aliphatic compounds

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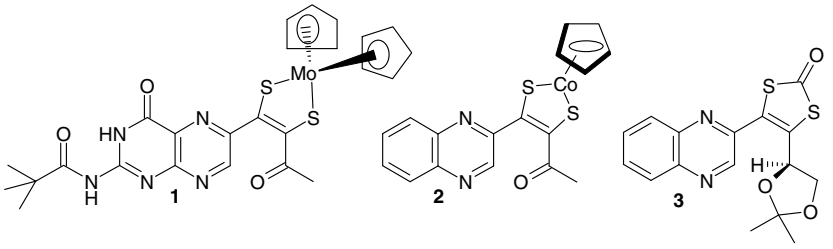
Abstract

A new, convenient and mild method for thioacetalization of heterocyclic, aromatic and aliphatic compounds catalyzed by $MoCl_5$ or MoO_2Cl_2 is described. This novel method is important for the synthesis of the difficult to prepare heterocyclic thioacetals such as the pterin thioacetals and it offers significant advantages such as high conversion, short reaction times and simplicity in operation.

Keywords: Heterocyclic aldehydes; 1,3-Propanedithiol; Thioacetalization; Heterocyclic thioacetals; Molybdenum pentachloride; Molybdenum dichloride dioxide

1. Introduction

Thioketal or thioacetal protection of carbonyl groups is of paramount importance in synthetic organic chemistry and hence, the development of novel thionation reactions remains of great interest. Heterocyclic molecules such as pterin[1,2] and quinoxaline[3,4] containing alkene-1,2-dithiolates (dithiolenes **1**, **2** and **3**) have received attention over the past 20 years owing to their interesting biochemistry and the complexation of transition metals, for example, molybdenum (present in nature as molybdenum cofactor[5]), tungsten and cobalt.



Although many different methods[6–10] have been reported in the literature for the preparation of thioacetals, the conversion of heterocyclic aldehydes to the corresponding thioacetals has so far received comparatively little success. Catalysts such as HCl,[11] PTSA,[12] BF_3–Et_2O,[13] $ZnCl_2$[14] and $AlCl_3$[15] have been reported for the preparation of thioketals and thioacetals, but these reagents fail to produce heterocyclic thioacetals. Despite the wide range of reagents available for the conversion of aldehydes to

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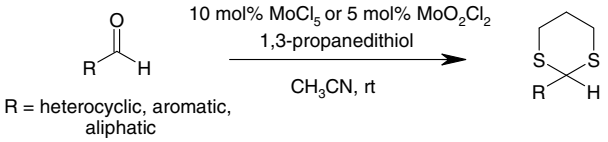
thioacetals, no attempt has been made to use molybdenum pentachloride or molybdenum dichloride dioxide as a catalyst. Recently, molybdenum dichloride dioxide was found to be very reactive in the catalytic thioglycosylation of O-acetylated glycosides with the functionalized thiols in methylene chloride.[16] Also, molybdenyl acetylacetonate[17] was found to be a good catalyst for the formation of oxathiolane, dithiolane and dithiane derivatives.

Fernandes et al. have shown that the high oxidation state in the molybdenum complex [MoO_2Cl_2] makes it a highly effective catalyst for organic reductions, such as the hydrosilylation of aldehydes and ketones,[18] and the reduction of imines,[19] esters, sulfoxides and pyridine N-oxides,[20] and for the epoxidation of double bonds and the oxidation of alcohols to carbonyl compounds.[21]

Consequently, we anticipated that $MoCl_5$ or MoO_2Cl_2 might catalyze the thioacetal formation from aldehydes as a result of the high oxidation states (+V or +VI) of molybdenum in these catalysts. We thus set out to establish a method (Scheme 1) for the transformation of heterocyclic, aromatic and aliphatic aldehydes to the corresponding thioacetals using $MoCl_5$ or MoO_2Cl_2 as a catalyst. We reacted several aldehydes with 1,3-propanedithiol in the presence of molybdenum pentachloride (10 mol %) or molybdenum dichloride dioxide (5 mol %) in dry acetonitrile as solvent at room temperature under a nitrogen atmosphere and obtained the corresponding thioacetal in excellent yield within a few minutes. This method is extremely useful for the synthesis of heterocyclic thioacetals (especially pterinthioacetal **4**) from the corresponding aldehydes. This method was also effective with acetals, for example, pterin or quinoxaline dimethylacetals (entries 8 and 9, Table 1). In these cases $MoCl_5$ was found to be more effective than MoO_2Cl_2. In contrast, MoO_2Cl_2 was a more effective catalyst with free aldehydes. Table 1 shows that polynuclear aromatic aldehydes undergo rapid transformation to the corresponding thioacetals in excellent yields compared to other aldehyde substrates. The reaction conditions and yields are summarized in Table 1. All the prepared compounds were characterized by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR and MS).

In summary, we have developed a novel method for the thioacetalization of heterocyclic, aromatic and aliphatic aldehydes to the corresponding dithianes with 1,3-propanedithiol and MoO_2Cl_2 or $MoCl_5$ as catalysts in moderate to excellent yields.



Scheme 1.

2. Typical experiment for the synthesis of quinoxalinthioacetal 5

To a stirred solution of quinoxaline aldehyde (500 mg, 3.16 mmol) and molybdenum pentachloride (10 mol %) or molybdenum dichloride dioxide (5 mol %) in acetonitrile (15 ml) cooled to 0–5 °C under a nitrogen atmosphere was added 1,3-propanedithiol (340 mg, 3.15 mmol) dropwise over 5 min with stirring and the mixture was then stirred at room temperature for 1.5 h. Water (50 ml) was added, and the organic product was extracted with methylene chloride (2 × 50 ml). The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography of the crude product on silica gel (100–200 mesh) and eluting with 0.5% methanol in methylene chloride afforded **5** as a brown crystalline solid (595 mg, 76%).

2.1. Compound 4

Mp 138–142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 13.34 (br s, 1H, NH), 9.03 (s, 1H), 8.82 (s, 1H), 5.34 (s, 1H), 3.13 (t, 2H, $J = 4.61$ Hz), 3.12, 3.02 (dd, 2H, $J = 2.68$, 2.96 Hz), 2.10–2.00 (m, 2H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 180.68, 159.36, 158.07, 154.12, 149.50, 141.64, 131.53, 54.45, 40.46, 27.0. MS (FAB): *m*/*z* (%): 367 (M^+, 50%). Anal. Calcd for $C_{15}H_{21}N_5O_2S_2$: C, 49.02; H, 5.75; S, 17.45. Found: C, 48.79; H, 5.64; N, 18.75; S, 17.46.

2.2. Compound 5

Mp 118–120 °C. FT-IR (KBr, *v*): 2924, 1660, 1493, 1364, 1275, 1202, 1126, 984, 912, 853 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 9.42 (s, 1H), 8.25–8.21 (m, 1H), 8.18–8.14 (m, 1H), 7.92–7.84 (m, 2H), 3.24 (t, 2H, $J = 9.64$ Hz), 3.20 (d, 1H, $J = 6.44$ Hz), 2.86–2.77 (m, 2H), 2.20–2.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 192.62, 145.24, 144.58, 140.96, 132.40, 131.06, 130.35, 129.47, 37.50, 36.92, 29.56. MS (FIA): *m*/*z* (%): 247 (M^+ 100%). Anal. Calcd for $C_{12}H_{12}N_2S_2$: C, 58.02; H, 4.87; N, 11.28; S, 25.82. Found: C, 58.09; H, 4.82; N, 11.16; S, 25.76.

2.3. Compound 6

Mp 127–128 °C. FT-IR (KBr, *v*): 2923, 1660, 1462, 1232, 1112, 918 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 8.30 (d, 1H, $J = 8.41$ Hz), 8.25 (d, 1H, $J = 6.40$ Hz), 8.05 (d, 1H, $J = 7.60$ Hz), 7.88 (d, 1H, $J = 7.61$ Hz), 7.79 (d, 1H, $J = 7.20$ Hz), 7.65 (d, 1H, $J = 7.20$ Hz), 3.25, 3.17 (td, 2H, $J = 4.21$, 4.01 Hz), 2.87–2.78 (m, 2H), 2.18–2.13 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 193.86, 151.59, 147.31, 137.40, 130.19, 129.50, 128.74, 127.72, 117.99, 117.10, 37.68, 31.15, 29.38. MS (FIA): *m*/*z* (%): 248 (MH^+, 20); 265 (M^+-1+H_2O, 62). Anal. Calcd for $C_{13}H_{13}NOS_2$: C, 63.12; H, 5.30; N, 5.66, S, 25.92. Found: C, 63.04; H, 5.41; N, 5.82; S, 26.08.

Table 1
Thioacetalization of heterocyclic, aromatic and aliphatic aldehydes using $MoCl_5$ or MoO_2Cl_2 as a catalyst

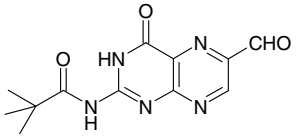
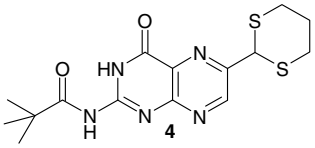
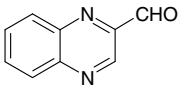
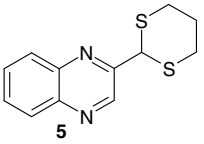
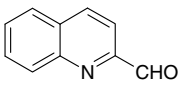
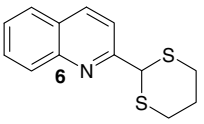
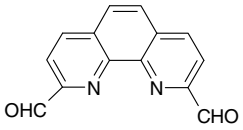
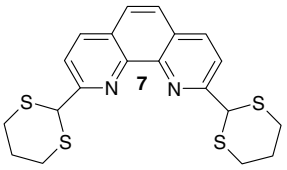
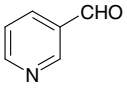
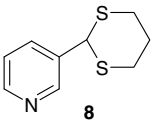
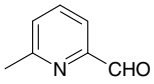
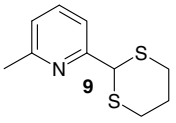
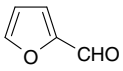
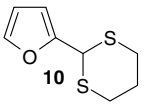
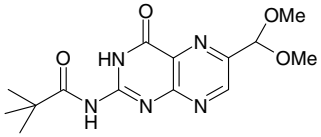
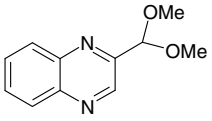
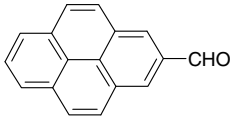
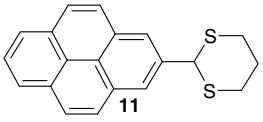
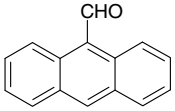
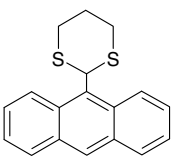
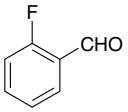
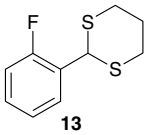
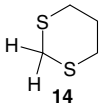
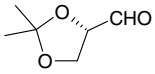
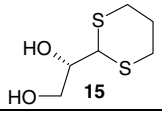
Entry	Substrate	Time[a] MoO_2Cl_2/$MoCl_5$	Products[b]	Yield[c] (%) MoO_2Cl_2/$MoCl_5$
1		2/3.5 h	 **4**	68/61
2		1.5/2 h	 **5**	76/64
3		1.5/3 h	 **6**	62/60
4		2/2.5 h	 **7**	64/61
5		2/3.5 h	 **8**	52/45
6		1/1.5 h	 **9**	55/52
7		30 min/1.5 h	 **10**	72/60
8		5/3.5 h	**4**	63/65
9		4/3.5 h	**5**	70/76
10		5/15 min	 **11**	92/82
11		8/25 min	 **12**	90/84

Table 1 (*continued*)

Entry	Substrate	Time[a] MoO_2Cl_2/$MoCl_5$	Products[b]	Yield[c] (%) MoO_2Cl_2/$MoCl_5$
12		30/45 min	 **13**	74/62
13		2.5/1 h	 **14**	62/55
14		30/45 min	 **15**	56/52

[a] Reactions were monitored by TLC analysis.
[b] All the known compounds (**8**,[10] **10**[10] and **14**[22]) and unknown products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.
[c] Yields refer to those of isolated pure products after column chromatography on a silica gel.

2.4. Compound 7

Mp 212–214 °C. FT-IR (KBr, *v*): 2924, 2923, 1675, 1412, 1230, 1156, 920, 802 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 8.25 (d, 2H, $J = 8.31$ Hz), 7.88 (d, 2H, $J = 8.25$ Hz), 7.81 (d, 2H, $J = 6.60$ Hz), 5.76 (s, 2H), 3.15 (t, 4H, $J = 5.56$ Hz), 2.26–2.23 (m, 4H), 2.11–2.04 (m, 4H). MS (FIA): *m*/*z* (%): 441 (M^++2+Na, 22); 311 (100). Anal. Calcd for $C_{20}H_{20}N_2S_4$: C, 57.65; H, 4.84; N, 6.72; S, 30.78. Found: C, 57.59; H, 4.77; N, 6.52; S, 30.65.

2.5. Compound 9

Semisolid. FT-IR (KBr, *v*): 2923, 1662, 1591, 1454, 1282, 1213, 947, 840 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.75 (d, 2H, $J = 7.56$ Hz), 7.70 (t, 2H, $J = 7.58$ Hz), 7.34 (d, 1H, $J = 7.40$ Hz), 3.15–3.01 (m, 2H), 2.80 (t, 2H, $J = 7.22$ Hz), 2.63 (s, 3H), 2.11–2.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 146.98, 132.95, 131.33, 129.82, 127.19, 31.87, 29.65, 29.65, 29.31. MS (FIA): *m*/*z* (%): 212 (MH^+, 17); 229 (M^++H_2O, 10).

2.6. Compound 11

Mp 195–197 °C. FT-IR (KBr, *v*): 2929, 1635, 1410, 1219, 1044, 834, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 8.54 (d, 2H, $J = 9.30$ Hz), 8.31 (d, 2H, $J = 8.04$ Hz), 8.21–8.15 (m, 3H), 8.05–8.00 (m, 2H), 6.22 (s, 1H), 3.29 (t, 2H, $J = 13.6$ Hz), 3.06, 3.02 (tt, 2H, $J = 3.52$, 3.51 Hz), 2.31–2.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 132.21, 131.31, 131.21, 130.63, 127.86, 127.27, 125.99, 125.91, 125.44, 125.24, 125.16, 124.91, 124.75, 122.65, 48.92, 32.82, 25.37. MS (FIA): *m*/*z* (%): 337 (M^+−1+H_2O, 21); 215 (100).

2.7. Compound 12

Mp 178–180 °C. FT-IR (KBr, *v*): 2925, 1668, 1445, 1420, 1271, 1156, 889, 719 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 9.48 (d, 1H, $J = 8.54$ Hz), 8.42 (s, 1H), 8.32 (d, 1H, $J = 8.61$ Hz), 7.99 (t, 1H, $J = 9.26$ Hz), 7.57 (d, 2H, $J = 6.24$ Hz), 7.46 (t, 2H, $J = 7.40$ Hz), 6.70 (s, 1H), 3.33 (t, 2H, $J = 12.0$ Hz), 3.07, 3.01 (tt, 2H, $J = 3.39$, 3.25 Hz), 2.35–2.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 131.86, 131.40, 130.70, 129.61, 129.47, 128.82, 128.67, 128.48, 128.13, 127.66, 126.68, 125.21, 124.74, 124.60, 122.74. MS (FIA): *m*/*z* (%): 313 (M^+−1+H_2O, 34); 191 (100).

2.8. Compound 13

Mp 65–66 °C. FT-IR (KBr, *v*): 2933, 1487, 1456, 1275, 1232, 1182, 1089, 784 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.61 (t, 1H, $J = 7.44$ Hz), 7.23 (d, 1H, $J = 6.89$ Hz), 7.12 (t, 1H, $J = 7.48$ Hz), 7.02 (t, 1H, $J = 9.10$ Hz), 3.09–3.03 (m, 2H), 2.88, 2.84 (tt, 2H, $J = 3.42$, 3.40 Hz), 2.13–2.09 (m, 1H), 1.94–1.83 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): 159.89, 157.43, 129.74, 126.14, 124.47, 115.17, 42.85, 31.95, 24.84. MS (FIA): *m*/*z* (%): 231 (M^++H_2O, 35); 109 (58).

2.9. Compound 15

Semi solid. FT-IR (KBr, *v*): 3384, 2916, 1675, 1422, 1075, 1038, 882, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 4.95 (d, 1H, $J = 1.80$ Hz), 3.99–3.74 (m, 2H), 3.74 (d, 1H, $J = 4.23$ Hz), 3.07 (br s, 1H), 2.98–2.86 (m, 2H), 2.73–2.65 (m, 2H), 2.35 (br s, 1H), 2.09–1.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 72.60, 63.63, 47.76, 29.66, 28.41, 25.50. MS (ESI): *m*/*z* (%): 281 (MH^+, 40).

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