Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 8001-8004, 1997

0040-4039/97 $17.00 + 0.00

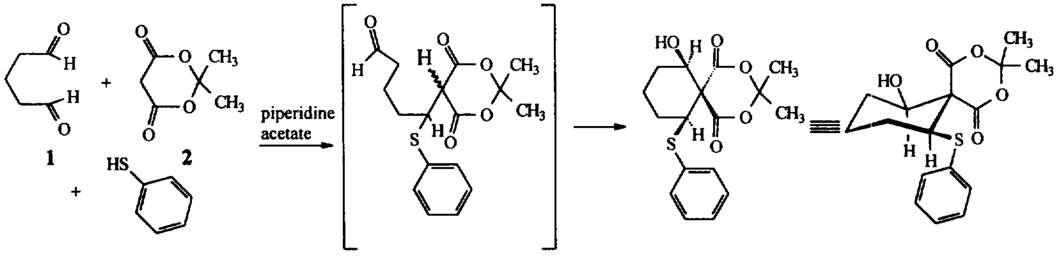
PII: S0040-4039(97)10174-5

Thioalkylation of Meldrum's Acid with Dialdehydes. Isopropylidene *cis*-2-Hydroxy-6-phenylthiocyclohexane-1,1-dicarboxylate Derivatives

Martin Eberle, Alex Ghorai and Richard G. Lawton*
The University of Michigan
Department of Chemistry
Ann Arbor, Michigan 48109-1055

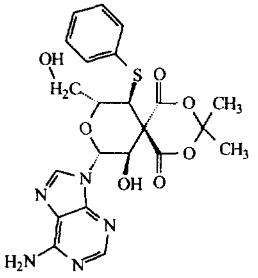
Abstract: Reaction of Meldrum's acid, thiophenol and gluteraldehyde in aqueous acetonitrile with piperidine acetate afffords a 70% yield of isopropylidene *cis*-2-hydroxy-6-phenylthiocyclohexane-1,1-dicarboxylate. The reaction is very general. It can be applied to dialdehydes derived in a many ways using many different thiols.
© 1997 Elsevier Science Ltd.

Gluteraldehyde [1], Meldrum's acid [2] and thiophenol [3] with 0.1% piperidinium acetate or proline react in aqueous acetonitrile at room temperature to give a 70% yield of a single adduct, isopropylidene *cis*-2-hydroxy-6-phenylthiocyclohexane-1,1-dicarboxylate[1] [5]. Other thiols, including *p*-thiocresol, thiolacetic acid, mercaptoethanol, *o*-mercaptobenzoic acid, *etc.*, may replace the thiophenol.[2] Often the spirocyclic product precipitates from the reaction mixture as the process proceeds. The reaction is also general for the dialdehyde component and has been used successfully with numerous substituted gluteraldehydes, o-phthalaldehyde, succindialdehyde and with a variety of dialdehydes derived through the periodate cleavage of sugars and nucleosides. The *cis* stereochemistry of hydroxyl and thioether elements was almost always preferred. Thus, the coupling constants[1] for H—C-2 and H—C-6 and a positive NOE observed for **5** on irradiation of H—C-2 for H—C-6 (and vice versa) established the *cis* relationship of the hydroxyl and phenylthio ether functions using the assumption of a chair-conformation with *equatorial* groups.

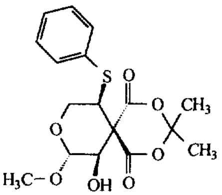


Scheme 1

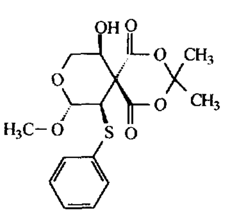
Although certain compounds containing an activated methylene group are known to undergo double aldol reactions with 1,4 and 1,5-dialdehydes to form respectively five and six-membered cyclic 1,3-subsititued ring systems, the reaction is severely restricted, always critically depending on the nature of the activating group(s). In the case of aliphatic dialdehydes, successful cyclizations have been previously limited to nitroalkanes[3] and malonic acid derivatives.[4] Meldrum's acid[5] [2] would seem to be an ideal component of this strategy, but in fact, previous attempts to condense dialdehydes with Meldrum's acid have been completely frustrated. The initial aldol product usually suffers dehydration followed by subsequent Michael addition of another Meldrum's acid and/or the elimination product then Michael adds to itself forming a dimer (γ to β site addition).[6] In practice, the diversity of available pathways yields a host of adducts. Our observation[7] that the intermediate dehydration product of the condensation of aldehydes with Meldrum's acid can be easily trapped by thiols to give synthetically useful adducts suggested the extrapolation of this same chemistry to dialdehydes. The mechanistic pathway with dialdehydes and thiols undoubtedly involves formation of an aldol intermediate of the aldehyde with Meldrum's acid. Dehydration is followed by Michael addition of the thiol component, trapping the intermediate **4**. The process is concluded by a second—now intramolecular—aldol to give cyclized product **5**. This last step is a reversible equilibrium.



6



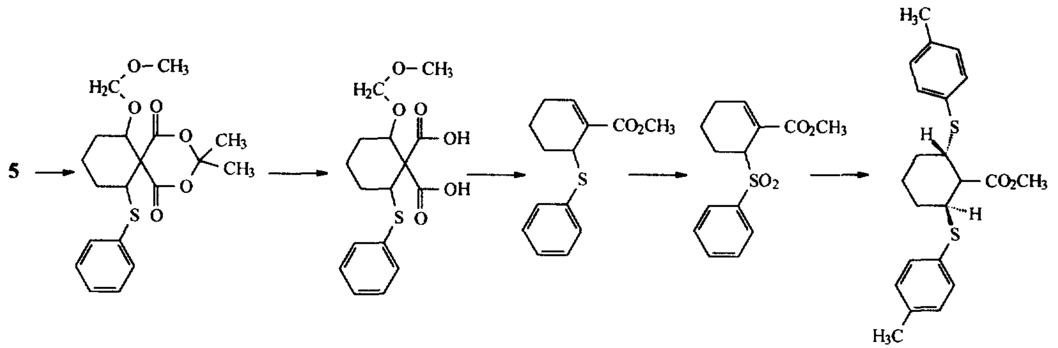
7



8

Adenosine upon periodate cleavage gives a dialdehyde that yields a single crystalline condensation product **6** with thiophenol and Meldrum's acid in 48% yield.[8] NMR experiments in both DMSO and d_6-acetone indicate the isomer isolated has the introduced phenylthioether and hydroxyl groups *cis* to one another with the hydroxymethyl function *trans* to the phenylthioether group. Reaction of the dialdehyde obtained through periodate cleavage of methyl β-D-xylopyranoside[9] gave a 51% yield of crystalline regioisomers **7**[10] and **8**[11] in a ratio of 4:1 (separated easily by flash chromatography). The regiochemistry of the two isomers was again determined by comparing the NMR-spectra of thioether and sulfone derivatives obtained through oxidation[12] of the thioethers by mCPBA and by NOE experiments.

iso-Propylidene *cis*-2-hydroxy-6-phenylthiocyclohexane-1,1-dicarboxylate [**5**] can be easily transformed to structures which serve as useful synthetic intermediates. Conversion to the corresponding MOM derivative **9**[13] [dimethoxymethane and P_2O_5 in $CHCl_3$[14]] followed by hydrolysis to the diacid **10** [KOH/ethanol, Scheme 2]. Decarboxylation with elimination and esterification[15] using DMF dimethyl acetal[16] affords methyl 6-phenylthiocyclohexene-1-carboxylate **11**[17] and this is easily oxidized to the corresponding sulfone **12**[18] using mCPBA. Unsaturated ester sulfone **12** undergoes the typical Michael-elimination-Michael sequence found with such functional group configurations.[19] Addition of *p*-toluenethiol [MeOH, Et_3N] to **12** yields methyl *trans*-2,6-*bis*(*p*-tolylthio)cyclohexanecarboxylate [**13**].[20] Both **12** and **13** are starting points for cyclic *e*quilibrium *t*ransfer *a*lkylation *c*ross-link [ETAC] chemistry.[19]



9 **10** **11** **12** **13**

Scheme 2

The exceptionally mild reaction conditions used in formation of the spiro cyclic adduct **5** are compatible with a large number of alternative functional groups, allowing almost any 1,4- or 1,5-dialdehyde and any thiol to be captured with Meldrum's acid. The technique is adaptable to the chemical modification and tethering of probes to carbohydrates, glycoproteins and carbohydrate containing biological and macromolecular materials.

REFERENCES and NOTES

1 **5**: Glutaraldehyde [**1**] (Aldrich, 2.5 M aqueous solution, 29.2 mL, 72.9 mmol), Meldrum's acid [**2**] (10.0 g, 69.4 mmol), thiophenol [**3**] (7.3 mL, 71.1 mmol), and piperidinium acetate are stirred in 100 mL acetonitrile. The product began spontaneously to crystallize after about 3 h. After 6 h, aqueous 5% citric acid (100 mL) was added and the solution was cooled to 5°. The product was filtered, washed with water and dried to yield 16.4 g (70%) of **5**. Crystallization from CH$_2$Cl$_2$/hexane. M.p. 151-153° dec. IR: 3441s, 2938w, 1765m, 1717s, 1445m, 1406m, 1395s, 1380s, 1299s, 1239m, 1231m, 1206m, 1080s, 1055s, 1043m, 1025m, 929m, 749m, 692m. ^{1}H-NMR (CDCl$_3$): 7.45-7.26 (m, 5H); 4.18 (dd, J = 4.8, 11.8, 1H, H-C(2)); 3.51 (dd, J = 4.5, 12.9, 1H, H-C(6)); 2.43 (br.s, 1H); 2.28-2.02 (m, 2H); 1.95-1.80 (m, 3H); 1.85 (s, 3H); 1.81 (s, 3H); 1.42-1.29 (m, 1H). NOE: between H-C(2) (5.5%) and H-C(6) (5%). ^{13}C-NMR (CDCl$_3$): 170.2; 164.4; 133.3; 133.0; 129.1; 128.2; 107.1; 60.5; 76.2; 53.0; 29.7; 29.5; 29.0; 28.9; 22.9. MS: 336 (M$^+$, 76), 279 (34), 261 (27), 169 (47), 151 (29), 150 (23), 110(88), 84 (27), 68 (35), 66 (37), 53 (26), 43 (100). Anal. calc. for C$_{17}$H$_{20}$O$_5$S : C 60.70, H 5.99, S 9.53, found C 60.79, H 6.04, S 9.48

2 Using the above procedure: 6-*p*-tolylthio derivative, mp 148-149°C; 6-acetylthio derivative, mp 122-124°C; 6-o-carboxyphenylthio derivative, mp 153°C ; 6-2-hydroxyethylthio derivative, mp 130-131°C.

3 a) Baer, H. H. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 67; b) Lichtenthaler, F. W. *Angew. Chemie* **1964**, *76*, 84. c) Padeken, H. G.; von Schickh, O.; Segnitz, A. *Houben-Weyl*, Bd. X/1 **1971**, *259*, 262. d) Angyal, S. J.; Gero, S. D. *Austr. J. Chem.* **1965**, *18*, 1973.

4 a) Lopez Aparicio, F. J.; Espinosa Ubeda, A.; Gallo Mezo, M. A. *An. Quim. Ser. C* **1976**, *72*, 981. b) Lopez Aparicio, F. J.; Espinosa Ubeda, A.; Gallo Mezo, M. A. *An. Quim. Ser. C* **1979**, *75*, 916.

5 For a review of Meldrum's acid chemistry see McNab, H. *Chem. Soc. Reviews* **1978**, *7*, 345.

6 Even simple Knoevenagel condensation of *n*-butyraldehyde with Meldrum's acid affords a double adduct. Margaretha, P.; Polansky, O. E.; *Tetrahedron Lett.* **1969**, 4983 reported the formation of a double adduct, mp 117-118°C. We believe the material isolated is in fact the dimer. See also Hedge, J. A.; Kunz C. W.; Snyder, H. R.. *J. Org. Chem.* **1961**, *26*, 3166; Eistert, B.; Geiss, F. *Ber.* **1961**, *94*, 929.

7 Eberle M.; Lawton, R. G. *Helv. Chim. Acta.* **1988**, *71*, 1974.

8 **6**: Mp 160° dec. IR: 3484m, 3341m, 3194m, 1763m, 1727s, 1640s, 1600m, 1394m, 1380m, 1359m, 1327m, 1304s, 1248m, 1205m, 1093m, 1083m. ^{1}H-NMR ((d$_6$)DMSO): 8.41 (s, 1H, adenosyl); 8.16 (s, 1H, adenosyl); 7.49 (d, J = 6.9, 2H); 7.38-7.27 (m, 3H); 7.22 (br. s, 2H); 6.91 (d, J = 6.0); 6.19 (d, J = 9.2, 1H); 4.89 (t, J = 6.0, 1H); 4.83 (dd, J = 6.0, 9.2, 1H); 4.45 (br. d, J = 10.8, 1H); 4.12 (d, J = 11.0,

1H); 3.79-3.68 (m, 2H); 1.83 (s, 3H); 1.77 (s, 3H); all protons bound to heteroatoms exchange with D_2O. ^{13}C-NMR ((d_6)DMSO): 168.1; 165.1; 156.1; 152.8; 150.0; 140.0; 133.3; 131.0; 129.5; 128.0; 107.8; 80.3; 78.3; 71.5; 61.2; 60.5; 50.4; 29.5; 29.3. MS (Cl): 153 (7) 137 (10); 136 (100). Anal. calc. for $C_{22}H_{23}N_5O_7S{\cdot}H_2O$: C 50.86, H 4.85, N 13.48, S 6.17; found C 50.85, H 4.85, N 13.50, S 6.15.

9 Cf. procedure of Baer, H.H.; Fischer, H.O. L. *J. Am. Chem. Soc.* **1959**, *81*, 5184.

10 **7**: M.p. 116° (sintering). $[\alpha]^D$= +26.7 (c = 2.5, $CHCl_3$). IR: 3401m, 1764m, 1733s, 1342s, 1305s, 1205m, 1104m, 1084s, 1044m, 995m, 743m. ^{1}H-NMR($CDCl_3$): 7.45-7.28 (m, 5H); 4.95 (d, *J* = 7.8, 1H); 4.31 (apparent t, *J* = 11.8, 1H); 3.96 (d, *J* = 7.8, 1H); 3.93 (dd, *J* = 5.5, 11.8, 1H); 3.83 (dd, *J* = 5.5, 11.8, 1H); 3.51 (s, 3H); 2.69 (br.s, 1H); 1.85 (s, 3H); 1.84 (s, 3H). ^{1}H-NMR ($d_6$benzene): 7.31-7.28 (m, 2H); 6.88-6.85 (m, 3H); 5.12 (d, *J* = 7.8, 1H); 4.56 (apparent t, *J* = 11.7, 1H); 4.18 (dd, *J* = 2.9, 7.8, 1H); 4.09 (dd, *J* = 5.5, 11.7, 1H); 3.94 (dd, *J* = 5.5, 11.7, 1H); 3.17 (s, 3H); 2.81 (d, *J* = 2.9, 1H); 1.52 (s,3H); 1.42 (s, 3H). ^{13}C-NMR ($CDCl_3$): 168.2; 164.6; 132.7; 132.2; 129.4; 128.6; 107.5; 100.9; 73.8; 66.0; 58.4; 57.0; 51.2; 29.6; 29.4. MS: 368 (M^+,13), 123 (100), 110 (50), 109(28), 97(31), 59 (38),45 (35),43(63).. Anal. calc. for $C_{17}H_{20}O_7S$: C 55.42, H 5.47, S 8.70; found C 55.33, H 5.56, S 8.69.

11 **8**: M.p. 111-112° (sintering). $[a]^D$ = -31.5 (c = 1.2, $CHCl_3$). IR: 3431s, 2850w, 1765m, 1732s, 1394m, 1381m, 1302s, 1206m, 1140m, 1089s, 1070s, 996m. ^{1}H-NMR ($CDCl_3$): 7.54-7.20 (m, 5); 5.15 (d, *J* = 8.7, 1H); 4.34 (dd, *J*=5.3, 10.3, 1H); 4.04 (dd, *J* = 10.3, 11.4, 1H); 3.89 (dd, *J* = 5.3, 11.4, 1H); 3.55 (d, *J* = 8.7, 1H); 3.54 (s, 3H); 2.88 (br. s, 1H); 1.92 (s, 3H); 1.82 (s, 3H). ^{13}C-NMR ($CDCl_3$): 168.3; 164.6; 134.2; 132.4; 129.0; 128.0; 107.7; 103.1; 72.1; 65.1; 61.3; 57.4; 30.2; 29.4. MS(CI): 387 (M^+ + 19, 12), 386 (M^+ + 18, 65), 278 (18), 276 (100), 258 (95). Anal. calc. for $C_{17}H_{20}O_7S$: C 55.42, H 5.47, S 8.70; found C 55.52, H 5.55, S 8.73.

12 The oxidation was performed on the NMR-sample by adding an excess of mCPBA

13 **9**: (84%) long needles. M.p. 103-104°C. IR: 1764m, 1734s, 1380m, 1294s, 1208m, 1099m, 1080m, 1042m, 1027s, 921m. ^{1}H-NMR ($CDCl_3$): 7.48-7.26 (m, 5H); 4.70 (d, *J* = 7.1, 1H); 4.53 (d, *J* = 7.1, 1H); 4.17 (apparent t, *J* = 6.6, central peak appears as t, *J* = 1.6, 1H); 3.58 (dd, *J* = 4.6, 12.9, 1H); 3.30 (s, 3H); 2.32-2.18 (m, 1H); 2.08-1.98 (m, 2H); 1.96-1.88 (m, 2H); 1.87 (s, 3H); 1.82 (s, 3H); 1.46-1.32 (m, 1H). ^{13}C-NMR ($CDCl_3$): 169.8; 163.8; 163.9; 133.3; 132.9; 129.1; 128.1; 106.8; 94.5; 8 0.5; 59.3; 55.9; 53.3; 29.6 (2 signals); 29.0; 25.1; 22.7. MS 380 (M^+, 1); 213 (4); 154(6); 109 (5); 79 (8); 45 (100); 43 (7). Anal. calc. for $C_{19}H_{24}O_6S$: C 59.98, H 6.36, S 8.43, found C 59.97, H 6.32, S 8.32

14 K. Fuji, S. Nakano, E. Fujita, *Synthesis* **1975**, 276.

15 Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**,1545.

16 Brechühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1965**, *48*, 1746.

17 **11**:^{1}H-NMR ($CDCl_3$): 7.54-7.51 (m, 2H); 7.30-7.23 (m, 3H); 7.06 (dd, *J* = 2.6, 4.8, 1H); 4.30-4.25 (br. apparent s, 1H); 3.77 (s, 3H); 2.38-1.97 (m, 4H); 1.76-1.66 (m, 2H).

18 **12**: M.p. 73°. IR: 2951m, 1716s, 1448m, 1301s, 1290m, 1265m, 1250s, 1141m, 728m. ^{1}H-NMR ($CDCl_3$): 7.89-7.49 (m, 5H); 7.26-7.25 (m, 1H); 4.37 (br. apparent d, 1H, *J* = 4.8, 1H); 3.44 (s, 3H); 2.56-2.52 (m,2H); 2.24-2.19 (m, 2H); 1.71-1.65 (m, 2H). ^{13}C-NMR ($CDCl_3$): 166.4; 147.0; 139.5; 133.6; 128.9; 123.7; 58.8; 51.8; 25.0; 22.0; 16.6 MS:281 (M^+ + 1,12), 249 (13), 139 (31), 138 (12), 137 (13), 107 (12), 80 (11), 79 (100), 78 (11), 77 (46), 59 (18), 51 (24). Anal. calc. for $C_{14}H_{16}O_4S$: C 59.98, H 5.75, S 11.44, found C 59.93, H 5.76, S 11.36.

19 a) Nelson, R. P.; McEuen, J. M.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 1225. b) Mitra, S.; Lawton, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 3097. c) Liberatore, F. A.; Comeau, R. D.; McKearin, J. M.; Pearson, D. A.; Belonga, B. Q.; Brocchini, S. J.; Kath, J.; Phillips, T.; Oswell, K.; Lawton, R. G. *Bioconjugate Chem.* **1990** *1*, 36. d) Pan, V.; Hutchinson, D. K.; Nantz, M. H.; Fuchs, P. L. *Tetrahedron* **1989**, *45*, 467

20 **13**: M.p. 148-149°C. ^{1}H-NMR ($CDCl_3$, 300MHz): 7.21 (ABq, *J* = 7.9, 6.8, 8H); 3.80 (s, 3H); 3.21 (m, *J* = 4.6, 1H); 3.04 (t, *J* = 4.3, 1H); 3.00 (t, *J* = 4.4, 1H); 2.33 (s, 6H); 2.17-2.00 (m, 2H); 2.00-1.89 (m, 1H); 1.80-1.75 (m, 2H); 1.41-1.23 (m, 1H). ^{13}C-NMR ($CDCl_3$, 360MHz): 171.4; 137.7; 138.4; 130.4; 129.7; 51.0; 49.5; 49.0; 27.0; 26.3; 21.1. Anal calc. for $C_{22}H_{26}O_2S_2$: C 68.35, H 6.78; found C 67.87, H 6.82.

(*Received in USA* 26 *August* 1997; *revised* 12 *September* 1997; *accepted* 13 *September* 1997)