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A SIMPLE SYNTHESIS OF 2,2-DISUBSTITUTED TETRAHYDROTHIOPHENES

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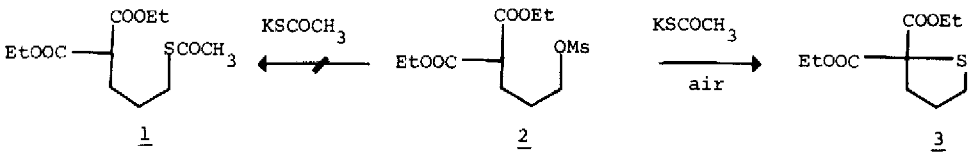
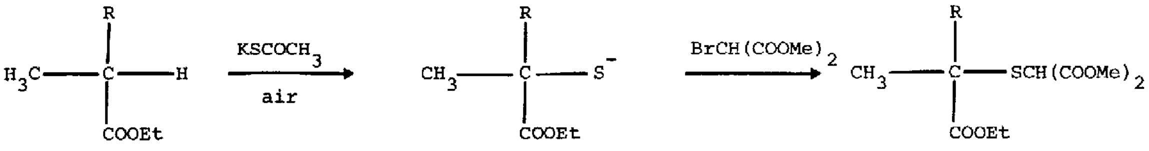
Treatment of diethyl 2-(3-mesyloxypropyl)malonate with $KSCOCH_3$/DMF at room temperature gave 2,2-dicarbethoxytetrahydrothiophene. The reaction can be used to prepare isopenams in good yield.



In an attempt to expand the scope of the recently reported synthesis of 2,2-dicarbalkoxytetrahydrofuran or pyrrolidines,[1] we attempted to prepare thioacetate 1 by treating mesylate 2 with 2.4 eq. of $KSCOCH_3$ in DMF at room temperature (7 hrs) without taking the precaution of carrying out the reaction in an inert atmosphere. Much to our surprise, a 90% yield of tetrahydrothiophene 3[2] was obtained. The reaction could be considerably accelerated by bubbling oxygen[3] through the reaction mixture. When care was taken to run the reaction in an oxygen-free atmosphere, only a small amount of 3 was obtained. In order to establish some of the features of this new reaction, the following reactions were carried out:

1. Reaction of mesylate 2 with 1.2 eq $KSCOCH_3$ in the presence of air gave ∿20-25% of tetrahydrothiophene 3, indicating that two equivalents of $KSCOCH_3$ were necessary for the reaction to proceed to completion.
2. Reaction of n-butyl mesylate with 2.4 eq of $KSCOCH_3$ in DMF in the presence of air or oxygen at room temperature led to nearly quantitative recovery of mesylate, even after 15 hrs, indicating clearly that a SN_2 displacement of mesylate by thioacetate did not take place under the reaction conditions.
3. Reaction of diethyl methylmalonate or ethyl 2-methylacetoacetate with

2.4 eq of KSCOCH$_3$ in DMF, followed by quenching with dimethyl 2-bromomalonate, gave a 50-60% yield of the corresponding sulfides 4a[4,5] and 4b[4]; this reaction shows clearly that either malonate anion or radical must react with some sulfur species.

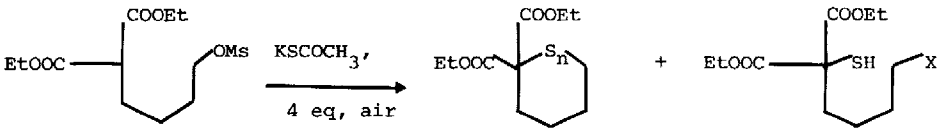


R = COOEt, COCH$_3$

4a, R = COOEt

4b, R = COOCH$_3$

4. Reaction of diethyl 2-(4-mesyloxybutyl)malonate[1] 5 with KSCOCH$_3$ (4 eq) in DMF in the presence of air at room temperature (25 hrs) gave a mixture of thiacyclohexane 6 (50%), dithiacycloheptane 7 (30%), and sulfhydryl malonates 8 (12%) and 9 (8%) as established by g.c.-chemical ionization mass spectroscopy only.[6]



5

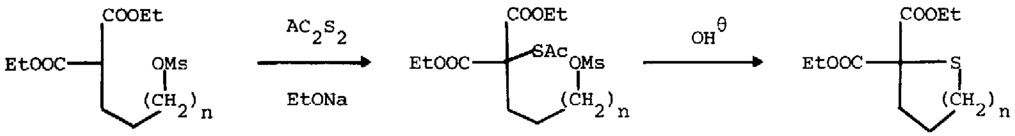
6, n = 1

7, n = 2

8, X = OMs

9, X = SCOCH$_3$

We suspected that some oxidized sulfur species was responsible for this reaction, and therefore treated mesylate 5 with (CH$_3$COS)$_2$[7] in DMF in a nitrogen atmosphere. This led to the formation of 10[5,8] in 30% yield. Treatment of 10 with 1% aqueous KOH in DMF gave 6 in 60% yield. Similarly, reaction of 2 with Ac$_2$S$_2$ (1 eq) and sodium ethoxide (1 eq) in DMF (2 hrs) in the absence of oxygen, gave a 42% yield of compound 11[5], which was hydrolyzed with 1 eq of 1% aqueous KOH in DMF, to give 3 in 85% yield.



5, n = 2

2, n = 1

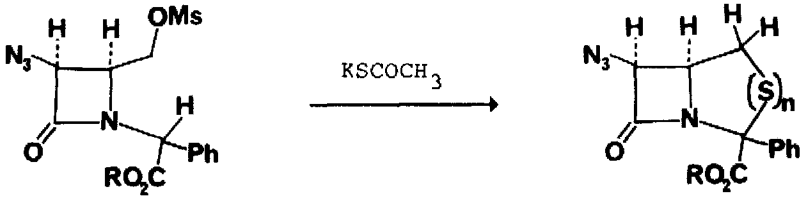
10, n = 2

11, n = 1

6, n = 2

3, n = 1

In order to prove the generality and mildness of this method, an epimeric mixture of β-lactam 12a[9] was reacted with 2.4 eq of $KSCOCH_3$ in DMF (10 hrs). A 70% yield of isopenam 13a[5,10] was obtained. When 12b[9] was treated with 4 eq of $KSCOCH_3$ for 15 hrs, a mixture of 13b[5,11] (60%) and 14b[5,12] (20%) was obtained, which were separated by column chromatography, using silica gel and CH_2Cl_2-$CHCl_3$ as eluents.



12 a, R = p-$CH_2C_6H_4NO_2$ 13, n = 1
b, R = Et 14, n = 2

It should be noted that prolonged reaction times also transformed the azido-group into an acetamide function. Thus, treatment of azidobenzene with $KSCOCH_3$ (2.4 eq) in DMF (48 hrs) at 20°, or in boiling butanone (12 hrs) gave acetanilide in excellent yield.

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References and Notes

1. G.H. Hakimelahi and G. Just, Tetrahedron Lett., 3645 (1979).
2. 3: ν 1731 cm^{-1}; δ 1.3 (6H, t, J = 7 Hz, CH_3CH_2O), 2.1 - 2.4 (4H, m, CH_2CH_2), 2.98 (2H, t, J = 6 Hz, CH_2S), 4.19 (4H, q, J = 7 Hz, CH_3CH_2O); M.S. m/e 232 ($C_{10}H_{16}O_4S$, S-cluster), 159 (M^+-COOEt, S-cluster), 113 (M^+-COOEt-H-OEt, S-cluster), 85 (113-CO, S-cluster); C.I. m/e 233 (M^++1, S-cluster), 159 (M^+-COOEt, S-cluster); Calcd. for $C_{10}H_{16}O_4S$, 51.72 H 6.89 S 13.79, found C 51.70 H 6.93 S 13.90.
3. Organic Chemistry of Sulfur, S. Oae, ed., Plenum Press, New York and London, 1953, p. 156.

4. 4b: ν 1745, 1715 cm^{-1}; δ 1.31 (3H, t, H = 7 Hz, CH_3CH_2O), 1.71 (3H, s, CH_3), 2.38 (3H, s, $COCH_3$), 3.79 (6H, s, $COOCH_3$), 4.1-4.4 (3H, q, J = 7 Hz, $CH_3\underline{CH_2}O$ and CH); C.I. m/e 233 (M^+-COOEt).
   4a: ν 1750 cm^{-1}; C.I. m/e 337 (M^++1), 263 (M^+-COOEt).
5. P.m.r. spectrum compatible with structure proposed.
6. 6: C.I. m/e 247 ($C_{11}H_{18}O_4S$+1, S-cluster), 173 (M^+-COOEt, S-cluster).
   7: C.I. m/e 279 ($C_{11}H_{18}O_4S_2$+1, S-cluster), 205 (M^+-COOEt, S-cluster).
   8: C.I. m/e 343 ($C_{12}H_{22}O_7S_2$+1, S-cluster), 297 (M^+-OEt), 215 (M^+-OMs-SH).
   9: C.I. m/e 291 (M^++1-S), 279 (M^+-$COCH_3$, S-cluster), 249 (M^+-COOEt, S-cluster), 247 (M^+-$SCOCH_3$).
7. B.M. Mikhailov and A.N. Blokhina, Doklady Akad. Nauk U.S.S.R. 80, 373-6 (1951); Chem. Abstr. 46, 5052c (1952).

8. 10: ν 1745, 1710 cm^{-1}; C.I. m/e 342 (M^++1-$COCH_3$, S-cluster), 296 (M^+-$COCH_3$-OEt); Calcd. for $C_{14}H_{24}O_8S_2$ C 43.75 H 6.25 S 16.64, found C 43.45 H 6.09 S 16.75.
9. G.H. Hakimelahi and G. Just, Can. J. Chem. 57, 1939 (1979).
10. 13a: ν 2105, 1780, 1735, 1525, 1345 cm^{-1}; C.I. m/e 398 ($C_{19}H_{15}N_5O_5S$+1-N_2, S-cluster), 343 (M^++1-N_3CHCO, S-cluster); Calcd. for $C_{19}H_{15}N_5O_5S$ C 53.64 H 3.52 N 16.47 S 7.52, found C 53.41 H 3.50 N 16.35 S 7.81.
11. 13b: ν 2105, 1780, 1730 cm^{-1}; C.I. m/e 319 ($C_{14}H_{14}N_4O_3S$+1, S-cluster), 291 (M^++1-N_2), 235 (M^+-N_3CHCO).
12. 14b: ν 2105, 1770, 1745 cm^{-1}; C.I. m/e 351 ($C_{14}H_{14}N_4O_3S_2$+1, S-cluster), 323 (M^++1-N_2).

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