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Alkylthioether Synthesis via Imidazole Mediated Mitsunobu Condensation

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Abstract: Unsymmetric alkylthioethers can be prepared from aliphatic thiols and unhindered alcohols under modified Mitsunobu conditions using trimethylphosphine/1,1'-(azodicarbonyl)dipiperdine (ADDP) in the presence of imidazole (2 equivalents).

Keywords: *Mitsunobu, thioethers, condensation, imidazole*

The Mitsunobu condensation[1] between an alcohol and a carboxylic acid or phenol has become a widely accepted synthetic procedure as a consequence of its exceptionally mild reaction conditions, simplicity, stereospecificity, and high yields. Variants of the Mitsunobu have emerged that extend its utility by replacing the traditional acidic component with alternative nucleophiles, e.g., halogens,[2] silanols,[3] amides/imides,[4] nitronates,[5] fluorinated alcohols,[6] and active methylenes.[7] For the formation of carbon-sulfur bonds, the most commonly exploited nucleophilic partners are acylthiols, thioamides, sulfenimides, thiophenols, and heteroaryl thiols.[4] Aliphatic thiols, in contrast, generally lack sufficient acidity to participate in Mitsunobu condensations.[8] Herein, we report an imidazole mediated Mitsunobu condensation of aliphatic thiols with unhindered alcohols for the facile synthesis of unsymmetric alkylthioethers (eq 1).

$$\mathbf{R'\text{–}SH} \;+\; \mathbf{HO\text{–}R} \xrightarrow[\mathbf{Im\text{-}H}]{\mathbf{Me_3P/ADDP}} \mathbf{R'\text{–}S\text{–}R} \qquad \textbf{(eq 1)}$$

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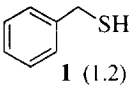
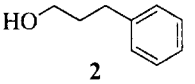
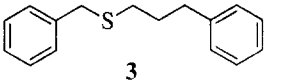
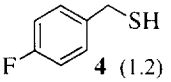
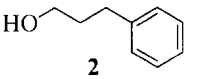
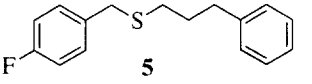
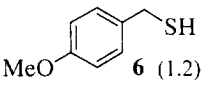
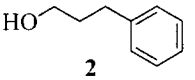
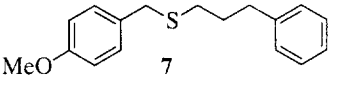
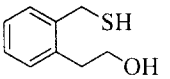
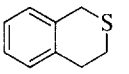
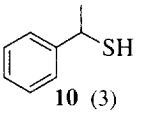
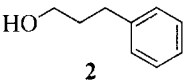
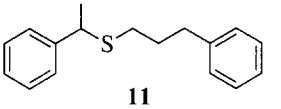
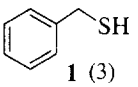
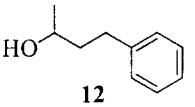
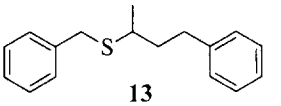
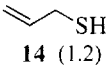
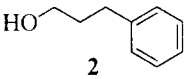
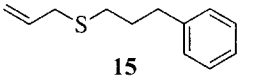
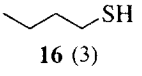
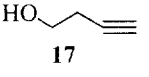
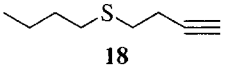
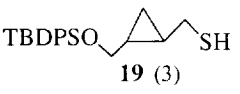
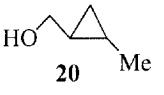
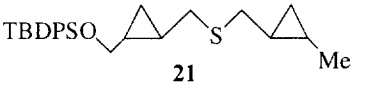
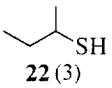
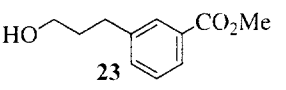
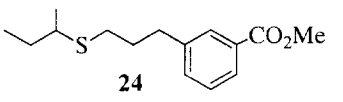
Table. Synthesis of Alkylthioethers

Entry	Thiol (equiv)	Alcohol	Alkylthioether	Yield (%)
1	 **1** (1.2)	 **2**	 **3**	79
2	 **4** (1.2)	 **2**	 **5**	86
3	 **6** (1.2)	 **2**	 **7**	75
4	 **8** (1)		 **9**	88
5	 **10** (3)	 **2**	 **11**	70
6	 **1** (3)	 **12**	 **13**	10
7	 **14** (1.2)	 **2**	 **15**	80
8	 **16** (3)	 **17**	 **18**	84
9	 **19** (3)	 **20**	 **21**	77
10	 **22** (3)	 **23**	 **24**	56

The scope of the procedure was assessed with a panel of representative thiols and the results are summarized in the Table. For the condensation between benzyl mercaptan (**1**) and 3-phenyl-1-propanol (**2**) to give thioether **3**,[9] the best results (Entry 1) were obtained using Me_3P/1,1'-(azodicarbonyl)dipiperdine[10] (ADDP) /imidazole (2 equiv each) in CH_2Cl_2 or THF at room temperature. Yields decreased sharply in Et_2O or in the absence of imidazole.[11,12] Tributylphosphine could replace the Me_3P with a ≈10-15% drop in efficiency. The major by-product was dibenzyl disulfide. Moderate electron withdrawing (Entry 2) and donating groups (Entry 3), represented by 4-fluorobenzyl mercaptan (**4**) and 4-methoxybenzyl mercaptan (**6**), respectively, had relatively minor influence on the outcome of the condensation and gave rise to the corresponding thioethers **5** and **7** in good yields. An intramolecular variant, i.e., **8**, was also successful and led to isothiochroman (**9**) (Entry 4). The secondary thiol **10** likewise provided a synthetically useful yield of thioether **11** (Entry 5), but only when the number of thiol equivalents was increased. On the other hand, the union of **1** with secondary alcohol **12** was sluggish even under forcing conditions and the yield of **13** rarely exceeded 10% (Entry 6).

Transformation of allyl mercaptan (**14**) to thioether **15**[9] (Entry 7) proceeded smoothly whereas the simple aliphatic thiols **16, 19,** and **22** proved a little less reactive. Their conversions to **18**, **21**, and **24**, respectively, were most conveniently conducted with 3 equiv of thiol in CH_2Cl_2. Importantly, the latter reactions demonstrated that the modified Mitsunobu conditions are compatible with a wide variety of functionality including acetylenes (Entry 8), silyl ethers (Entry 9), and esters (Entry 10).

General Procedure

Trimethylphosphine (2 mmol; 1 M solution in toluene, Aldrich Chem. Co.) was added dropwise under an argon atmosphere to a stirring, room temperature solution of alcohol (1 mmol), ADDP (2 mmol), and imidazole (2 mmol) in CH_2Cl_2 or THF (15 mL). After stirring overnight, an equal volume of hexane was added and any precipitate was removed by filtration. All volatiles were evaporated *in vacuo* and the residue was purified to give the corresponding alkylthioether in the indicated yields (Table).

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References and Notes

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2. For example, see: Manna, S.; Falck, J. R.; Mioskowski, C. *Syn. Comm.* **1985**, *15*, 663-668.
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6. Falck, J. R.; Yu, J.; Cho, H.-S. *Tetrahedron Lett.* **1994**, *35*, 5997-6000.
7. For example, see: Yu, J.; Cho, H.-S.; Falck, J. R. *J. Org. Chem.* **1993**, *58*, 5892-5894.
8. Cf., Tanigawa, T.; Kanamaru, H.; Murahashi, S.-I. *Tetrahedron Lett.* **1975**, 4655-4658.
9. ^{1}H NMR (400 MHz, $CDCl_3$) for **3**: δ 7.10-7.42 (m, 10 H), 3.69 (s, 3 H), 2.67 (t, J ~7.5 Hz, 2 H), 2.42 (t, J ~7.3 Hz, 2 H), 1.80-1.98 (m, 2 H); ^{13}C NMR: 141.47, 138.46, 128.75, 128.40, 128.28, 126.82, 125.81, 36.06, 34.71, 30.73, 30.52. ^{1}H NMR for **15**: 7.17-7.32 (m, 5 H), 5.69-5.86 (m, 1 H), 4.99-5.04 (m, 2 H), 3.11 (dt, J ~7.2 and 1.06 Hz, 2 H), 2.71 (t, J ~7.8 Hz, 2 H), 2.47 (t, J ~7.5 Hz, 2 H), 1.82-1.95 (m, 2 H)); ^{13}C NMR: 30.97, 31.89, 35.67, 35.85, 117.86, 126.90, 129.37, 129.50, 135.43, 142.61.
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11. The utility of imidazole in mediating Mitsunobu condensations has been noted: Lai, J.-Y.; Yu, J.; Hawkins, R. D.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5691-5694.
12. Modest yields of thioethers could be obtained from benzylic mercaptans in refluxing THF in the absence of imidazole.