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TETRAHEDRON

(Cyanomethyl)trimethylphosphonium iodide as reagent for the intermolecular *S*-alkylation of thiols with alcohols

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Abstract—Treatment of mixtures of thiols and primary aliphatic alcohols with (cyanomethyl)trimethylphosphonium iodide leads to the clean formation of unsymmetric thioethers. The required phosphonium iodide is simple to prepare and stable towards air and moisture. This new synthesis of thioethers yields crude products of high purity and should be suitable for parallel solution-phase chemistry.

1. Introduction

The *S*-alkylation of thiols either by treatment with alkylating agents or with alcohols under the conditions of the Mitsunobu reaction[1] are the most common approaches to the synthesis of thioethers. Few alkylating agents with interesting pharmacophoric groups are, however, commercially available, and many of them are toxic. Alcohols, on the other hand, are usually stable and easy to handle, and can be purchased with a broad variety of additional functional groups. For this reason, alcohols are ideal building blocks for the production of compound libraries.[2]

As part of a program directed towards the development of new strategies for the preparation of compound libraries, we have been seeking a reagent, which would convert aliphatic alcohols into alkylating agents, even in the presence of other nucleophiles. Such a reagent could be used to alkylate these nucleophiles directly with alcohols in a one-pot procedure. Of particular interest would be a reagent, which could mediate the direct, intermolecular alkylation of amines[3] and thiols with aliphatic alcohols. We recently reported[4] that (cyanomethyl)trialkylphosphonium iodides efficiently mediate the *N*-alkylation of aliphatic amines with alcohols. This discovery led to the development of a practical, one-step synthesis of tertiary amines from aliphatic alcohols and secondary aliphatic amines.[4] I now wish to disclose a new synthesis of thioethers, which is also based on the use of (cyanomethyl)trimethylphosphonium iodide as condensing agent.

2. Results and discussion

Treatment of an equimolar mixture of a primary aliphatic alcohol and an aliphatic or aromatic thiol with a slight excess of (cyanomethyl)trimethylphosphonium iodide and diisopropylethylamine (DIPEA) in propionitrile at 90–95°C led to clean formation of the corresponding thioethers. Illustrative examples are listed in Table 1. The reaction required heating and the presence of a tertiary amine to proceed to completion. Aromatic thiols generally gave higher yields than aliphatic ones (e.g. **4d**), which is probably due to the lower acidity of the latter. We assume that the fair yields (Table 1) were also due to losses during recrystallization. The only by-products observed resulted from the *N*-alkylation of benzimidazoles, but this side-reaction took place to a significant degree only when aliphatic thiols (**4d**) or an excess of alkylating agent (**4b**) were used. Secondary alcohols did not undergo the reaction.

A proposed mechanism for this reaction is shown in Scheme 1. It has been reported[5] that some stabilized phosphorus ylides react with alcohols to yield ethers, presumably via alkoxyphosphonium alkoxides such as **7** (Scheme 1). (Cyanomethyl)phosphonium salts (pK_{HA} 7[6]) can be deprotonated by diisopropylethylamine (DIPEA), and can then react with alcohols to yield intermediates **6**.[7] Thermolysis of the latter in the presence of DIPEA hydroiodide leads to P–C bond cleavage and release of acetonitrile, to yield alkoxyphosphonium iodides **7**, which are known to decompose smoothly to yield alkyl iodides **8**.[8] These finally should react with thiols to yield the observed thioethers **4**.

The main advantages of this new synthesis of thioethers, when compared to the Mitsunobu reaction,[1] are its simplicity of performance and isolation of the products (see Section 3). Only one reagent (**3**) is required, and the only by-products formed are trimethylphosphinoxide and DIPEA

Keywords: alcohols; alkylation; phosphonium salts; thioethers.

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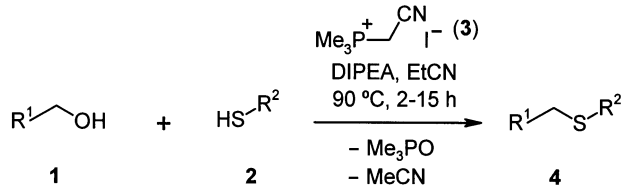
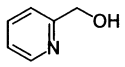
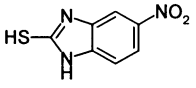
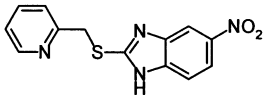
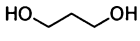
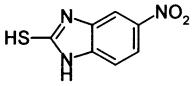
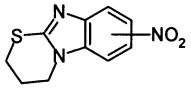
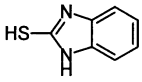
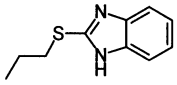
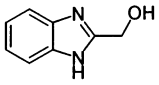
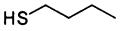
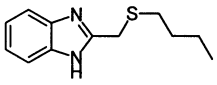
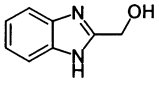
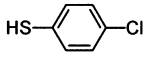
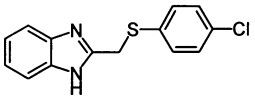
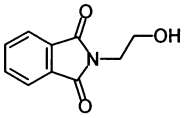
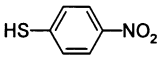
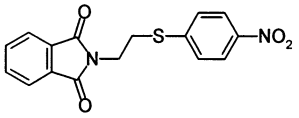
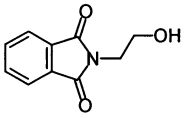
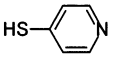
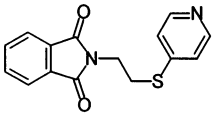
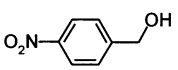
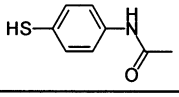
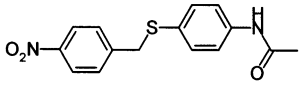
Table 1. Phosphonium iodide mediated alkylation of thiols by alcohols



Entry	Alcohol 1	Thiol 2	Thioether 4	Yield[a]
a				84%
b				71%[b]
c				81%
d				38%[c]
e				68%
f				64%
g				54%
h				76%

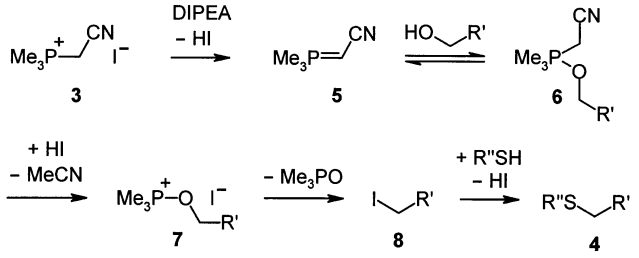
Phosphonium salt **3** (1.2 equiv.) and diisopropylethylamine (DIPEA, 1.3 equiv.) were added to an equimolar mixture of the alcohol and the thiol (both 1.0 equiv., 0.40 mol L^{-1}) in dry propionitrile. The mixture was stirred at 90–95°C for 2–15 h.

[a] Yields of recrystallized products.

[b] 2.4 equiv. of **3** and 2.6 equiv. of DIPEA were used, and an equimolar mixture of two regioisomers was obtained.

[c] 4 equiv. of 1-butanethiol was used to supress the competing *N*-alkylation of the benzimidazole.

hydroiodide, which are easily removed during aqueous workup. All the products listed in Table 1 could be isolated by a simple extraction, and the crude products were sufficiently pure for direct biological testing. Because of these advantages this new synthesis of thioethers should also be well suited for automated, parallel synthesis both in solution and on solid phase.



Scheme 1. Proposed mechanism for the alkylation of thiols by alcohols with the aid of (cyanomethyl)trimethylphosphonium iodide **3**.

We conclude that reagent **3** efficiently promotes the intermolecular *S*-alkylation of thiols with alcohols. Phosphonium iodide **3** is easy to prepare[4] and to handle, and does not react with air, water, or alcohols at room temperature. We found this reagent to offer a convenient alternative to synthetic protocols, in which an alcohol is first converted into an alkylating agent, which is then used to alkylate thiols or amines in a second step.

3. Experimental

All solvents and reagents were used as purchased, and propionitrile was stored over molecular sieves (0.3 nm).

3.1. General procedure for the alkylation of thiols with alcohols

3.1.1. 5-Nitro-1*H*-benzimidazol-2-yl 2-pyridylmethyl sulfide (4a). The phosphonium iodide **3**[4,9] (299 mg, 1.23 mmol) was added to a mixture of 2-(hydroxymethyl)-pyridine (146 mg, 1.34 mmol; **1a**), 5-nitrobenzimidazole-2-thiol (196 mg, 1.00 mmol; **2a**), DIPEA (0.25 mL, 1.41 mmol), and propionitrile (3.0 mL), and the mixture was stirred at 92°C for 14 h. The mixture was allowed to cool to room temperature, water (30 mL) was added, and the product was extracted with dichloromethane (3×12 mL). The combined organic layers were washed with brine (20 mL), dried with magnesium sulfate, and concentrated under reduced pressure. Recrystallization from acetonitrile yielded 240 mg (84%) of the title compound as yellow crystals: mp 194–195°C; HPLC-MS *m/z* 287 [MH^+]; ν_{max}(KBr) 3085–2600 (br), 1621, 1591, 1570, 1510 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.76 (s, 2H), 7.29–7.35 (m, 1H), 7.56–7.67 (m, 2H), 7.75–7.82 (m, 1H), 8.08 (dd, J=8 Hz, 1 Hz, 1H), 8.34 (br s, 1H), 8.54–8.59 (m, 1H), 13.38 (br s, 1H). Anal. calcd for $C_{13}H_{10}N_4O_2S$ (286.31): C, 54.54; H, 3.52; N, 19.57. Found: C, 54.65; H, 3.51; N, 19.46.

Using the same procedure as for **4a**, the following thioethers were prepared.

3.1.2. 7/8-Nitro-3,4-dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine (4b). From 5-nitrobenzimidazole-2-thiol (274 mg, 1.40 mmol) and 1,3-propanediol (108 mg, 1.42 mmol) was obtained 233 mg (71%) of **4b** as equimolar mixture of two isomers. Yellow crystals, mp 204–227°C (MeCN); HPLC-MS *m/z* 236 [MH^+]; ν_{max} (KBr) 1612, 1592, 1516, 1459, 1422 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.31–2.41 (m, 2H), 3.35–3.40 (m, 2H), 4.29–4.39 (m, 2H), 7.60 (d, J=9 Hz, 0.5H), 7.65 (d, J=9 Hz, 0.5H), 8.06–8.12 (m, 1H), 8.30 (br s, 0.5H), 8.43 (br s, 0.5H). Anal. calcd for $C_{10}H_9N_3O_2S$ (235.27): C, 51.05; H, 3.86; N, 17.86. Found: C, 51.12; H, 3.87; N, 17.75.

3.1.3. 1*H*-Benzimidazol-2-yl propyl sulfide (4c). From 2-mercaptobenzimidazole (152 mg, 1.01 mmol) and 1-propanol (66 mg, 1.11 mmol) was obtained 157 mg (81%) of **4c** as colorless crystals: mp 164–165°C (MeCN); HPLC-MS *m/z* 193 [MH^+]; ν_{max}(KBr) 3054–2600 (br), 1505, 1432, 1395, 1346 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.99 (t, J=7 Hz, 3H), 1.73 (sext, J=7 Hz, 2H), 3.25 (t, J=7 Hz, 2H), 7.08–7.14 (m, 2H), 7.32–7.39 (m, 1H), 7.47–7.53 (m, 1H), 12.49 (s, 1H). Anal. calcd for $C_{10}H_{12}N_2S$ (192.28): C, 62.47; H, 6.29; N, 14.57. Found: C, 62.50; H, 6.27; N, 14.50.

3.1.4. 1*H*-Benzimidazol-2-ylmethyl butyl sulfide (4d). An excess of thiol (4 equiv.) was required to supress *N*-alkylation of the benzimidazole. From 1-butanethiol (0.86 mL, 8.01 mmol) and 2-(hydroxymethyl)benzimidazole (302 mg, 2.04 mmol) was obtained 170 mg (38%) of **4d** as colorless needles: mp 145–146°C (MeCN; Lit.[10]: 144°C); HPLC-MS *m/z* 221 [MH^+]; ν_{max}(KBr) 2962–2533 (br), 1455, 1437, 1275, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (t, J=7 Hz, 3H), 1.32 (sext, J=7 Hz, 2H), 1.49 (quint, J=7 Hz, 2H), 2.54 (t, J=7 Hz, 2H), 3.89 (s, 2H), 7.11–7.17 (m, 2H), 7.49 (br s, 2H), 12.33 (br s, 1H). Anal. calcd for $C_{12}H_{16}N_2S$ (220.34): C, 65.41; H, 7.32; N, 12.71. Found: C, 64.78; H, 7.42; N, 13.00.

3.1.5. 1*H*-Benzimidazol-2-ylmethyl 4-chlorophenyl sulfide (4e). From 4-chloro-1-benzenethiol (244 mg, 1.69 mmol) and 2-(hydroxymethyl)benzimidazole (222 mg, 1.50 mmol) was obtained 278 mg (68%) of **4e** as colorless crystals: mp 187–188°C (MeCN); HPLC-MS *m/z* 275 [MH^+]; ν_{max}(KBr) 2912–2400 (br), 1474, 1438, 1404, 1273 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.45 (s, 2H), 7.12–7.17 (m, 2H), 7.33–7.38 (m, 2H), 7.41–7.55 (m, 4H), 12.44 (s, 1H). Anal. calcd for $C_{14}H_{11}ClN_2S$ (274.77): C, 61.20; H, 4.04; N, 10.20. Found: C, 61.31; H, 4.09; N, 10.17.

3.1.6. 4-Nitrophenyl 2-(*N*-phthalimidoyl)ethyl sulfide (4f). From 4-nitro-1-benzenethiol (155 mg, 1.00 mmol) and *N*-(2-hydroxyethyl)phthalimide (192 mg, 1.00 mmol) was obtained 210 mg (64%) of **4f** as yellow crystals: mp 180–183°C (MeCN); ν_{max}(KBr) 1765, 1711, 1576, 1503, 1420 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.45 (t, J=7 Hz, 2H), 3.88 (t, J=7 Hz, 2H), 7.56 (d, J=9 Hz, 2H), 7.80–7.88 (m, 4H), 8.07 (d, J=9 Hz, 2H). Anal. calcd for $C_{16}H_{12}N_2O_4S$ (328.35): C, 58.53; H, 3.68; N, 8.53. Found: C, 58.85; H, 3.70; N, 8.58.

3.1.7. 2-(*N*-Phthalimidoyl)ethyl 4-pyridyl sulfide (4g). From 4-mercaptopyridine (110 mg, 0.99 mmol) and *N*-(2-hydroxyethyl)phthalimide (192 mg, 1.00 mmol) was obtained 152 mg (54%) of **4g** as light-brown crystals: mp 148–149°C (MeCN); HPLC-MS *m/z* 285 [MH^+]; ν_{max}(KBr) 1765, 1706, 1576, 1396, 1356 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.37 (t, J=7 Hz, 2H), 3.86 (t, J=7 Hz, 2H), 7.33 (m, 2H), 7.82–7.40 (m, 4H), 8.36 (m, 2H). Anal. calcd for $C_{15}H_{12}N_2O_2S$ (284.34): C, 63.36; H, 4.25; N, 9.85. Found: C, 63.46; H, 4.31; N, 9.92.

3.1.8. 4-Acetamidophenyl 4-nitrobenzyl sulfide (4h). From 4-acetamido-1-benzenethiol (334 mg, 2.00 mmol) and 4-nitrobenzylalcohol (309 mg, 2.02 mmol) was obtained 461 mg (76%) of **4h** as yellow crystals: mp 181–182°C (MeCN); HPLC-MS *m/z* 303 [MH^+]; ν_{max}(KBr) 3308, 1662, 1586, 1516, 1347 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.02 (s, 3H), 4.28 (s, 2H), 7.27 (d, J=9 Hz, 2H), 7.48–7.54 (m, 4H), 8.13 (d, J=9 Hz, 2H), 9.97 (s, 1H). Anal. calcd for $C_{15}H_{14}N_2O_3S$ (302.35): C, 59.59; H, 4.67; N, 9.27. Found: C, 59.61; H, 4.73; N, 9.24.

Acknowledgements

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References

1. (a) Falck, J. R.; Lai, J.-Y.; Cho, S.-D.; Yu, J. *Tetrahedron Lett.* **1999**, *40*, 2903–2906. (b) Hughes, D. L. *Org. Prep. Proc.* **1996**, *28*, 127–164.
2. (a) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000. (b) Zaragoza, F.; Stephensen,

H. *Angew. Chem. Int. Ed. Engl.* **2000**, *112*, 565–567. (c) Zaragoza, F.; Stephensen, H. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 554–556.
3. Zaragoza, F.; Stephensen, H. *Tetrahedron Lett.* **2000**, *41*, 1841–1844.
4. Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518–2521.
5. (a) Grayson, M.; Keough, P. T. *J. Am. Chem. Soc.* **1960**, *82*, 3919–3924. (b) Pappas, J. J.; Gancher, E. *J. Org. Chem.* **1966**, *31*, 1287–1289.
6. Zhang, X.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968–972.
7. The isolated (cyanomethylene)phosphorane **5** has been used with success for Mitsunobu-type chemistry: Itô, S.; Tsunoda, T. *Pure Appl. Chem.*, **1999**, *71*, 1053–1057. Phosphorane **5** is, however, sensitive towards air and moisture, and is more difficult to prepare and to handle than phosphonium iodide **3**.
8. Rydon, H. N. In *Org. Synth. Coll. Vol. 6*, Wiley-VCH, 1973; pp 830–832.
9. Currier, H. C.; Sherr, A. E.; Klein, H. G. US Patent 3654342, 19 Aug. 1968; *Chem. Abstr.*, **1973**, *77*, 20631z.
10. Sekikawa, I. *Bull. Chem. Soc. Jpn* **1958**, *31*, 252–254.