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Catalysis by an ionic liquid: efficient conjugate addition of thiols to electron deficient alkenes catalyzed by molten tetrabutylammonium bromide under solvent-free conditions

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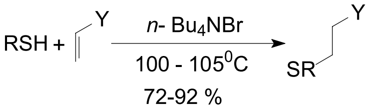
Abstract—An inexpensive and readily available ionic liquid, tetrabutylammonium bromide in the molten state, efficiently catalyzes the conjugate addition of thiols to α,β-unsaturated nitriles, carboxylic ester, ketones and aldehydes as well as nitro olefins. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The conjugate addition of nucleophiles to electron deficient alkenes is one of the most effective methods for carbon–carbon bond formation and has many applications in organic synthesis.[1] Among various nucleophilic additions, the reaction of thiols is of much importance as it leads to the synthesis of compounds with promising biological activities.[2] Usually, this conjugate addition is based either on the activation of thiols by a base[3] or activation of the acceptor olefins with Lewis acids.[4] We report here an efficient conjugate addition of a thiol to an activated alkene catalyzed by molten tetrabutylammonium bromide without any solvent (Scheme 1). Recently, the use of ionic liquids as solvent and catalyst has attracted much attention in the context of green synthesis.[5]

However, high cost of most of the conventional room temperature ionic liquids and apprehension regarding the toxicity of some of them has led to the use of more benign salts in the molten state as practical alternatives. Recently, molten tetrabutylammonium bromide was used as an efficient catalyst in a number of useful synthetic transformations by us[6a] and other groups.[6b–d]



Scheme 1.

2. Results and discussion

The experimental procedure for the reaction is very simple: A mixture of alkene and thiol was added to molten tetrabutylammonium bromide (15 mol%) at 100–105°C and was stirred at that temperature for 1–2 h as required to complete the reaction. The reaction mixture was extracted with ether and the crude product was purified by column chromatography to furnish the pure adduct. The tetrabutylammonium bromide remaining in the reaction flask was washed with hexane, dried under vacuum and was recycled for subsequent uses without any loss of efficiency.

Both aromatic and aliphatic thiols react with a variety of conjugated alkenes by this procedure to produce the corresponding adducts in high yields. The results are summarized in Table 1. The conjugated alkenes include α,β-unsaturated nitriles, carboxylic esters, ketones and aldehydes as well as nitro olefins. These reactions catalyzed by molten tetrabutylammonium bromide are in general, very fast and clean. The crude products obtained are virtually pure and a 'short' column chromatography gave analytically pure sample. No addition was observed using solid tetrabutylammonium bromide at room temperature. Also, reaction in the absence of tetrabutylammonium bromide at 100–105°C leads to a mixture of unidentified products. Thus, the presence of molten tetrabutylammonium bromide is essential for an efficient and clean reaction. The amount of tetrabutylammonium bromide may be reduced to as little as 15 mol%; however, a higher amount may be used. Presumably, molten tetrabutylammonium bromide acts as a

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Keywords: thiol; alkene; tetrabutylammonium bromide; conjugate addition; solvent-free reaction.

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Table 1. Addition of thiol to alkenes catalyzed by molten tetrabutylammonium bromide

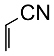
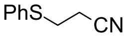
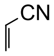
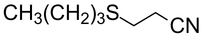
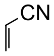
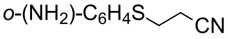
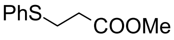
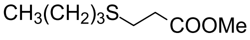
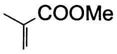
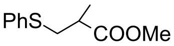
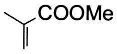
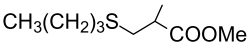
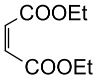
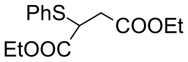
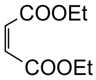
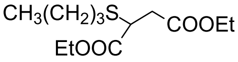
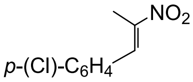
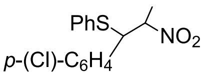
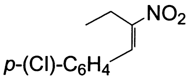
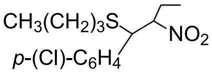
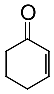
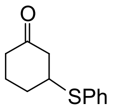
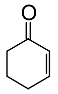
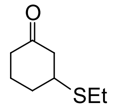
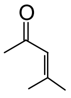
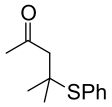
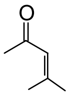
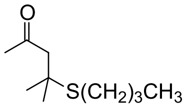
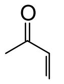
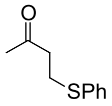
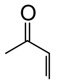
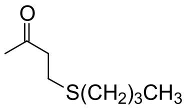
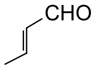
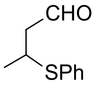
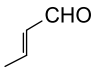
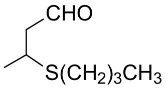
Entry	Thiol	Alkene	Time (h)	Product	Yield (%)[a]
1	PhSH		1.0		92
2	*n*-BuSH		1.5		88
3	*o*-$(NH_2)-C_6H_4SH$		0.5		90
4	PhSH		1.0		92
5	*n*-BuSH		1.5		90
6	PhSH		2.0		85
7	*n*-BuSH		2.0		87
8	PhSH		0.75		90
9	*n*-BuSH		1.5		87
10	PhSH		2.0		91
11	*n*-BuSH		2.0		88
12	PhSH		0.5		92

Table 1 (*continued*)

Entry	Thiol	Alkene	Time (h)	Product	Yield (%)[a]
13	EtSH		0.75		90
14	PhSH		2.0		78
15	*n*-BuSH		2.5		81
16	PhSH		2.0		72
17	*n*-BuSH		2.0		70
18	PhSH		1.0		90
19	*n*-BuSH		1.5		89

[a] Yields refer to those of pure isolated products characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

ready source of bromide ion, which is hydrogen-bonding to the thiol increasing the nucleophilicity of sulfur atom. This makes the thiolate anion a better nucleophile leading to efficient addition to conjugated alkenes.

3. Conclusion

In conclusion, the reported procedure of the conjugate addition of thiols to electron-deficient alkenes under solvent-free conditions demonstrates the potential of molten tetrabutylammonium bromide, a benign readily available ionic liquid as an efficient and recyclable catalyst and has much promise for further applications. Moreover, this methodology offers significant improvements with regard to yield of products, simplicity in operation, cost efficiency and green aspects avoiding toxic catalysts and solvents.

4. Experimental

4.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in $CDCl_3$ solutions. IR spectra were taken as neat. Elemental analyses were done by a Perkin–Elmer auto-analyzer. Column chromatography was performed on silica gel (60–120 mesh, SRL, India). Thiols and conjugated alkenes are mostly commercial materials and were distilled before use. Tetrabutylammonium bromide (Lancaster, UK) was also recrystallized before use.

4.1.1. General procedure for conjugate addition of thiols to alkenes: representative procedure for the synthesis of 1-cyano-2-thiophenylethane (entry 1). A mixture of thiophenol (242 mg, 2.2 mmol) and acrylonitrile (106 mg, 2 mmol) was added to molten tetrabutylammonium bromide (97 mg, 0.30 mmol, 15 mol%) and the whole mixture was stirred at 105°C (oil bath) for 1 h as indicated by TLC for a complete reaction. The reaction mixture was then allowed to cool to room temperature and extracted with ether (3×25 mL). The ether extract was washed with water and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the crude product over silica gel (hexane/ether 97:3) furnished the pure 1-cyano-2-thiophenyl ethane as a colorless oil (300 mg, 92%), whose spectroscopic data (IR and NMR) are identical to those reported.[7]

This procedure was followed for all the reactions listed in Table 1. The compounds that are known are identified by comparison of their spectroscopic data with those reported in the literature (however, a few known compounds reported in entries 2,5,8,9 whose spectroscopic data are not available for comparison are also properly characterized by their spectroscopic data). The IR, ^1H and ^{13}C NMR spectral data and elemental analysis, confirms the identities of new compounds. All these data are furnished below in order of their entries in Table 1.

4.1.2. 1-Cyano-2-thiobutylethane (entry 2). Colorless oil;[8] IR 2929, 2250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.79 (t, J=7.1 Hz, 2H), 2.66–2.57 (m, 4H), 1.63–1.54 (m, 2H), 1.48–1.36 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 118.8, 32.4, 31.9, 28.1, 22.3, 19.3, 14.0.

4.1.3. 1-Cyano-2-(2-aminothiophenyl)ethane (entry 3). Colorless oil.[9]

4.1.4. Methyl 3-thiophenylpropionate (entry 4). Colorless oil.[10]

4.1.5. Methyl 3-thiobutylpropionate (entry 5). Colorless oil;[11] IR 2956, 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.7 (s, 3H), 2.78 (t, J=7.2 Hz, 2H), 2.61 (t, J=7.2 Hz, 2H), 2.53 (t, J=7.4 Hz, 2H), 1.62–1.52 (m, 2H), 1.47–1.37 (m, 2H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 172.8, 52.1, 35.1, 32.2, 31.9, 27.3, 22.3, 14.0.

4.1.6. Methyl 2-methyl-3-thiophenylpropionate (entry 6). Colorless oil.[7b]

4.1.7. Methyl 2-methyl-3-thiobutylpropionate (entry 7). Colorless oil; IR 2956, 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 3H), 2.75 (dd, J=12.2, 6.2 Hz, 1H), 2.60–2.40 (m, 4H), 1.49–1.42 (m, 2H), 1.35–1.25 (m, 2H), 1.17 (d, J=6.8 Hz, 3H), 0.83 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 176.0, 52.1, 40.6, 35.9, 32.7, 32.1, 22.3, 17.2, 14.0. Anal. calcd for $C_9H_{18}SO_2$: C, 56.80; H, 9.53. Found: C, 56.63; H, 9.39.

4.1.8. Diethyl 2-thiophenylsuccinate (entry 8). Colorless oil;[12] IR 2976, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.28 (m, 5H), 4.15–4.06 (m, 4H), 4.00–3.96 (m, 1H), 2.97–2.87 (m, 1H), 2.74–2.66 (m, 1H), 1.26–1.15 (m, 6H); ^{13}C NMR δ 171.5, 170.9, 134.5 (2C), 132.2, 129.4 (2C), 129.1, 61.8, 61.3, 46.1, 36.9, 14.5, 14.4.

4.1.9. Diethyl 2-thiobutylsuccinate (entry 9). Colorless oil;[13] IR 2954, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02–3.86 (m, 4H), 3.39 (dd, J=9.9, 5.6 Hz, 1H), 2.73 (dd, J=9.9, 16.9 Hz, 1H), 2.49–2.36 (m, 3H), 1.36–1.27 (m, 2H), 1.21–0.98 (m, 8H), 0.66 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 172.2, 171.1, 61.7, 61.3, 41.91, 36.9, 31.6, 31.5, 22.3, 14.5 (2C), 13.9.

4.1.10. 3-(4-Chlorophenyl)-2-nitro-2-thiophenylpropane (entry 10). Colorless oil (1:1 mixture of diastreoisomers); IR 2958, 1552, 1490, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 14H), 7.16–7.08 (m, 4H), 5.03–4.91 (m, 2H), 4.61 (d, J=12.2 Hz, 1H), 4.58 (d, J=12.2 Hz, 1H), 1.89 (d, J=6.7 Hz, 3H), 1.46 (d, J=6.7 Hz, 3H); ^{13}C NMR (2 sets of peaks) δ 136.5, 135.5, 134.6, 134.5 (2C), 134.4 (2C), 134.3 (2C), 132.1 (2C), 130.1 (2C), 129.7 (2C), 129.6 (2C), 129.4 (2C), 129.2 (3C), 129.1 (2C), 87.0, 86.4, 57.1, 56.5, 18.6, 17.8. Anal. calcd for $C_{15}H_{14}ClSNO_2$: C, 58.53; H, 4.58; N, 4.55. Found: C, 58.36; H, 4.39; N, 4.41.

4.1.11. 4-(4-Chlorophenyl)-3-nitro-4-thiobutylbutane (entry 11). Colorless oil (1:1 mixture of diastreoisomers); IR 2958, 1556, 1490, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.41 (m, 8H), 4.90–4.77 (m, 2H), 4.36 (d, J=10.6 Hz, 1H), 4.34 (d, J=10.6 Hz, 1H), 2.56–2.38 (m, 5H), 2.38–2.21 (m, 1H), 2.13–1.88 (m, 1H), 1.68–1.61 (m, 4H), 1.52–1.46 (m, 4H), 1.19 (t, J=7.4 Hz, 3H), 1.07–0.99 (m, 9H); ^{13}C NMR (2 sets of peaks) δ 136.9 (2C), 134.4, 134.3, 130.0 (2C), 129.9 (2C), 129.6 (2C), 129.3 (2C), 94.5, 94.2, 52.0, 51.7, 31.9, 31.5, 31.4, 31.3, 26.4, 26.3, 22.2, 22.1, 13.9 (2C), 10.7, 10.6. Anal. calcd for $C_{14}H_{20}ClSNO_2$: C, 55.71; H, 6.68; N, 4.64. Found: C, 55.59; H, 6.51; N, 4.48.

4.1.12. 3-Thiophenylcyclohexanone (entry 12). Colorless oil.[3a]

4.1.13. 3-Thioethylcyclohexanone (entry 13). Colorless oil.[14]

4.1.14. 4-Methyl-4-thiophenylpentan-2-one (entry 14). Colorless oil.[15]

4.1.15. 4-Methyl-4-thiobutylpentan-2-one (entry 15). Colorless oil; IR 2958, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 2H), 2.53 (t, J=7.2 Hz, 2H), 1.57–1.38 (m, 4H), 1.41 (s, 6H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 206.9, 55.0, 43.6, 32.6, 31.9, 28.9 (2C), 28.1, 22.7, 14.1. Anal. calcd for $C_{10}H_{20}SO$: C, 63.78; H, 10.70. Found: C, 63.59; H, 10.61.

4.1.16. 4-Thiophenylbutan-2-one (entry 16). Colorless oil.[15]

4.1.17. 4-Thiobutylbutan-2-one (entry 17). Colorless oil.[16]

4.1.18. 3-Thiophenylbutanal (entry 18). Colorless oil.[17]

4.1.19. 3-Thiobutylbutanal (entry 19). Colorless oil; IR 2958, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, J=1.7 Hz, 1H), 3.23–3.14 (m, 1H), 2.61–2.43 (m, 4H), 1.52–1.42 (m, 2H), 1.37–1.24 (m, 2H), 1.21 (d, J=6.9 Hz, 3H), 0.82 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 200.9, 50.8, 34.4, 32.0, 30.5, 22.4, 22.2, 13.9. Anal. calcd for $C_8H_{16}SO$: C, 59.95; H, 10.06. Found: C, 59.79; H, 9.89.

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