Indium(I) Iodide-Promoted Cleavage of Dialkyl Disulfides and Subsequent Michael Addition of Thiolate Anions to Conjugated Carbonyl Compounds

Brindaban C. Ranu,* Tanmay Mandal

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta – 700 032, India
Fax +91(33)24732805; E-mail: ocbcr@iacs.res.in

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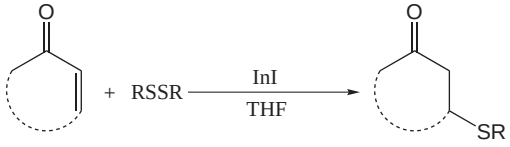
Abstract: Indium(I) iodide promotes cleavage of dialkyl disulfides generating thiolate anions which then undergo facile addition to α,β-unsaturated ketones, aldehydes, carboxylic esters and nitriles under neutral conditions producing corresponding β-keto or β-cyano sulfides in high yields. There are several examples of dialkyl/diaryl disulfides and activated alkenes participating in this reaction.

Key words: indium(I) iodide, dialkyl disulfide, Michael addition, β-keto sulfide, β-cyano sulfide

During last few years tremendous achievement has been observed in the use of indium metal and its derivatives, particularly trihalides for carbon-carbon bond formation, various novel rearrangements and many other useful transformations.[1] This success has led to a continued search for newer indium derivatives for novel applications.[2] As a part of our interest in indium chemistry[1e,3] we have initiated an investigation on the use of less explored indium(I) iodide[4] for useful chemical transformation.[5] We wish to disclose here a facile cleavage of dialkyl disulfides using InI in THF and subsequent addition of dithiolate anion to conjugated enones and nitriles in one pot without any other reagent (Scheme 1).

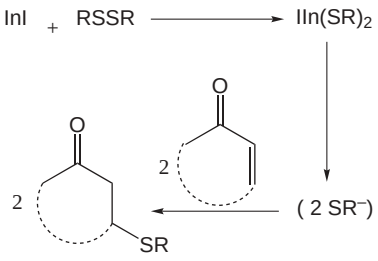


Scheme 1

The experimental procedure is very simple.[6] A solution of dialkyl disulfide and activated alkene in THF was heated under reflux in presence of indium(I) iodide and the product was isolated by usual workup. A wide range of α,β-unsaturated ketones, aldehydes and carboxylic esters underwent facile Michael additions to dithiolate anions generated by the cleavage of disulfides by this procedure to provide the corresponding adducts in high yields. Conjugated nitriles are also found to react with the thiolate anions although the yields are relatively low compared to those with carbonyl compounds. The results are summarized in Table 1. Aliphatic as well as aromatic disulfides are found to undergo cleavage and subsequent reaction. On the other hand, both cyclic and acyclic conjugated carbonyl compounds participate in this reaction as Michael acceptors.

The reactions are, in general, very clean, fast and high yielding. IR, ^{1}H and ^{13}C NMR spectral data, easily identified the products by comparison with the literature values.[8,9] It is speculated that the reaction is going through the intermediacy of bis(thioalkyl)iodoindium(III) (**1**) which then releases thiolate anion to be trapped by the Michael acceptor (Scheme 2).

In conclusion, this one-pot procedure provides an efficient methodology for the Michael addition of thiolate anion to activated alkenes through an indium(I) iodide-mediated cleavage of dialkyl disulfides. In contrast to the usual Michael addition of thiols to conjugated carbonyl compounds in presence of strong alkali where the yields are often lower due to dimerization of thiols,[7] this procedure offers a neutral reaction medium and a novel approach and thus presents a practical alternative to the existing procedures for the synthesis of β-keto sulfides.[7,8] Moreover, this procedure demonstrates the synthetic potential of indium(I) iodide and leaves great promise for more useful applications.



Scheme 2

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Table 1 InI-Mediated Cleavage of Disulfides Followed by Michael Addition

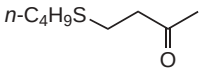
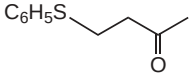
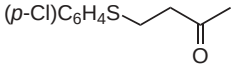
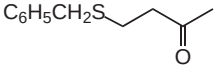
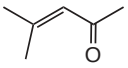
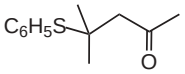
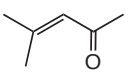
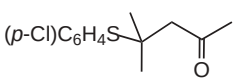
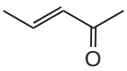
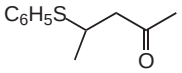
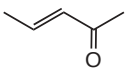
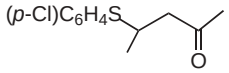
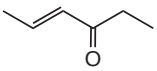
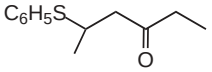
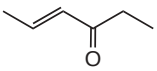
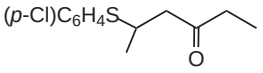
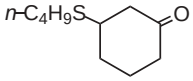
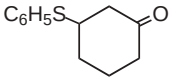
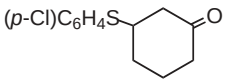
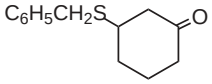
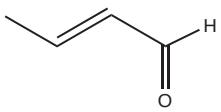
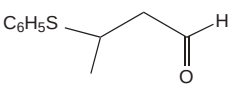
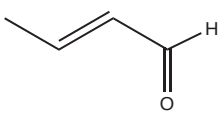
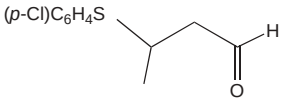
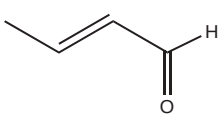
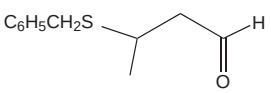
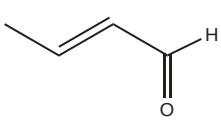
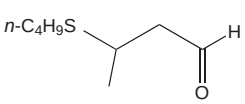
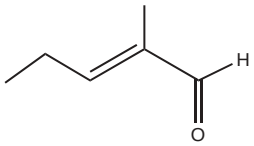
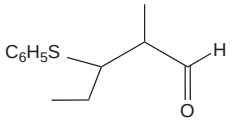
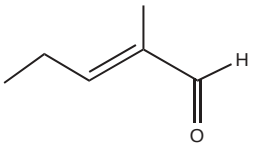
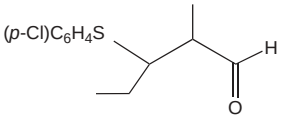
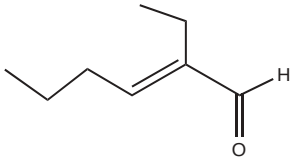
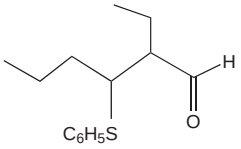
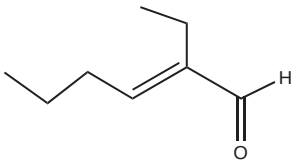
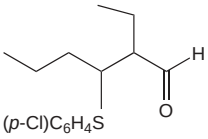
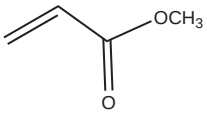
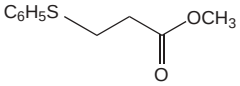
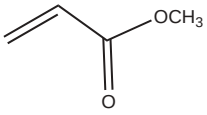
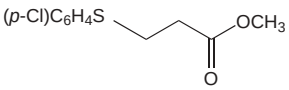
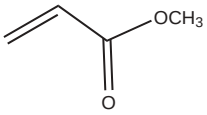
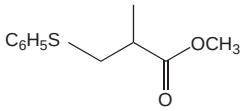
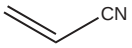
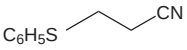
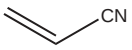
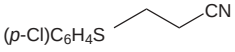
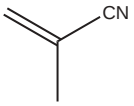
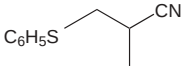
Entry	Disulfide	Substrate	Time (h)	Product	Yield (%)[a]	Ref.
1	*n*-C_4H_9S-S*n*-C_4H_9		3.0		85	8c
2	C_6H_5S-SC_6H_5		2.5		86	9
3	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		2.5		85	
4	$C_6H_5CH_2$S-S$CH_2C_6H_5$		3.0		82	8e
5	C_6H_5S-SC_6H_5		2.5		85	8b
6	(*p*-Cl)C_6H_4S-SC6H_4(*p*-Cl)		3.0		81	
7	C_6H_5S-SC_6H5		2.5		82	
8	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		3.0		80	
9	C_6H_5S-SC_6H_5		2.25		80	
10	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		3.0		78	
11	*n*-C_4H_9S-S*n*-C_4H_9		2.5		90	8b
12	C_6H_5S-SC_6H_5		1.5		95	8e
13	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		2.0		92	8d
14	$C_6H_5CH_2$S-S$CH_2C_6H_5$		2.5		89	8e
15	C_6H_5S-SC_6H_5		2.5		92	8b
16	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		3.0		90	
17	$C_6H_5CH_2$S-S$CH_2C_6H_5$		3.5		82	
18	*n*-C_4H_9S-S*n*-C_4H_9		4.0		80	8b

Table 1 InI-Mediated Cleavage of Disulfides Followed by Michael Addition (continued)

Entry	Disulfide	Substrate	Time (h)	Product	Yield (%)[a]	Ref.
19	C_6H_5S-SC_6H_5		3.0		80 (61:39)[b]	
20	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		3.5		78 (59:41)[b]	
21	C_6H_5S-SC_6H_5		3.0		80 (53:47)[b]	
22	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		3.5		76 (51:49)[b]	
23	C_6H_5S-SC_6H_5		4.0		73	8b
24	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		4.25		70	
25	C_6H_5S-SC_6H_5		5.0		60	8b
26	C_6H_5S-SC_6H_5		4.0		72	8b
27	(*p*-Cl)C_6H_4S-SC_6H_4(*p*-Cl)		4.5		65	
28	C_6H_5S-SC_6H_5		5.0		55	

[a] Yields refer to those of pure isolated products characterized by spectroscopic data (IR, ^{1}H and ^{13}C NMR).
[b] Ratio of diastereoisomers as determined by ^{1}H NMR.

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(6) **General Experimental Procedure**; **Representative Example for the Cleavage of Diphenyl Disulfide and Subsequent Reaction with Methyl Vinyl Ketone (Entry 2)**: Indium(I) iodide (121 mg, 0.5 mmol) was added to the solution of diphenyl disulfide (109 mg, 0.5 mmol) in freshly distilled THF (2.5 mL) under argon atmosphere followed by the addition of methyl vinyl ketone (70 mg, 1 mmol). The reaction mixture was heated under reflux for 2.5 h (TLC). THF was then evaporated off and the residue was quenched with water and extracted with Et_2O (3 × 10 mL). The Et_2O extract was washed with water and dried (Na_2SO_4). The aqueous extract containing indium derivatives was discarded although in relatively large-scale reactions indium salts may be recovered. Evaporation of the solvent left the crude product, which was purified by column chromatography over silica gel (hexane–Et_2O, 95:5) to provide the pure addition product, 4-thiophenylbutan-2-one (155 mg, 86%) as a colorless liquid. IR (neat): 1716, 1477 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3 H), 2.76 (t, *J* = 7.26 Hz, 2 H), 3.13 (t, *J* = 7.26 Hz, 2 H), 7.20–7.22 (m, 2 H), 7.26–7.35 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 30.5, 43.5, 126.7, 127.9, 129.4 (2 × C), 130.0 (2 × C). These values are in good agreement with those reported for this compound.[9] Several Michael adducts are known and are identified by comparison of their spectroscopic data with those reported. The new compounds are characterized by their spectroscopic data and elemental analysis. These data for a few selective representative compounds are provided here.
Entry 8: IR (neat): 1475, 1716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.51 Hz, 3 H), 2.12 (s, 3 H), 2.55 (dd, J_1 = 8.34 Hz, J_2 = 17.22 Hz, 1 H), 2.72 (dd, J_1 = 5.31 Hz, J_2 = 17.19 Hz, 1 H), 3.65 (m, 1 H), 7.26 (d, *J* = 8.61 Hz, 2 H), 7.33 (d, *J* = 8.61 Hz, 2 H). ^{13}C NMR (75 MHz): δ = 20.9, 30.5, 38.4, 50.0, 129.0 (2 × C), 132.5, 133.4, 133.6 (2 × C), 206.2. Anal. Calcd for $C_{11}H_{13}OClS$: C, 57.76; H, 5.73. Found: C, 57.84; H, 5.81.
Entry 17: IR (neat): 1477, 1724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.75 Hz, 3 H), 2.55–2.61 (m, 2 H), 3.13–3.19 (m, 1 H), 3.78 (s, 2 H), 7.24–7.33 (m, 5 H), 9.66 (s, 1 H). ^{13}C NMR (75 MHz): δ = 21.3, 33.6, 35.2, 50.1, 127.1, 128.5 (2 × C), 128.7 (2 × C), 137.9, 200.5. Anal. Calcd for $C_{11}H_{14}OS$: C, 68.0; H, 7.26. Found: C, 68.09; H, 7.17.
Entry 20: Obtained as a mixture of diastereoisomers (59:41). IR (neat): 1475, 1724, 2721 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.17 Hz, 3 H), 1.20 (d, *J* = 7.21 Hz, 3 H), 1.62–1.73 (m, 2 H), 2.63–2.67 (m, 1 H), 3.34–3.40 (m, 1 H), 7.26 (d, *J* = 8.34 Hz, 2 H), 7.37 (d, *J* = 8.34 Hz, 2 H), 9.67 (d, *J* = 1.59 Hz, 1 H, minor), 9.68 (d, *J* = 0.98 Hz, 1 H, major). ^{13}C NMR (75 MHz): δ = 9.7 (major), 10.2 (minor), 12.1 (major), 11.8 (minor), 26.2 (major), 24.2 (minor), 48.9 (major), 49.6 (minor), 52.9 (major), 51.7 (minor), 129.1 (2 × C), 133.4, 133.5 (2 × C), 133.6, 203.2. Anal. Calcd for $C_{12}H_{15}OClS$: C, 59.37; H, 6.23. Found: C, 59.41; H, 6.17.
Entry 24: IR (neat): 1477, 1737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.59 (t, *J* = 7.5 Hz, 2 H), 3.13 (t, *J* = 7.5 Hz, 2 H), 3.67 (s, 3 H), 7.19–7.29 (m, 4 H). ^{13}C NMR (75 MHz): δ = 29.7, 34.4, 52.3, 129.5 (2 × C), 131.8 (2 × C), 134.1, 134.2, 172.4. Anal. Calcd for $C_{10}H_{11}O_2ClS$: C, 52.06; H, 4.77. Found: C, 52.11; H, 4.71.

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