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Iodine as novel reagent for the 1,2-addition of trimethylsilyl cyanide to ketones including α,β-unsaturated ketones

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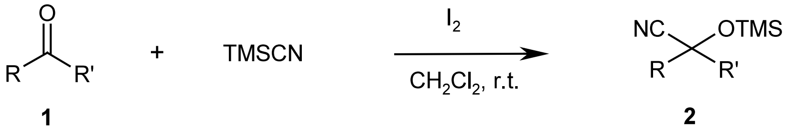
Abstract—Molecular iodine is found to catalyze efficiently the addition of trimethylsilyl cyanide to a range of simple and functionalized ketones under very mild and convenient conditions to afford the corresponding cyanohydrin trimethylsilyl ethers in excellent yields in a short reaction period with high selectivity. α,β-Unsaturated ketones selectively afford the corresponding 1,2-adducts without the formation of 1,4-adducts under similar reaction conditions. © 2002 Elsevier Science Ltd. All rights reserved.

α-Cyanohydrins or cyanohydrin trimethylsilyl ethers are useful precursors for the synthesis of α-hydroxy-acids, α-hydroxyaldehydes, β-aminoalcohols, α-cyanoketones and many other types of compounds.[1] They are generally prepared by the nucleophilic addition of cyanide to carbonyl compounds.[2] Among various cyanating agents such as potassium or sodium cyanide and HCN, the use of trimethylsilyl cyanide is safe and a more effective cyanide anion source for nucleophilic addition to carbonyl compounds under mild conditions.[3] Generally, in the absence of a catalyst, no reaction is observed between TMSCN and carbonyl compounds. Consequently, several activators or promoters both in stoichiometric and catalytic amounts have been reported for the cyanation of carbonyl compounds with trimethylsilyl cyanide.[4,5] Recently, lanthanide triflates were also reported to be efficient catalysts in promoting cyanation reactions of carbonyl compounds.[6] However, only few methods have been reported for the cyanation of substituted and functionalized ketones.[7] Furthermore, many of these methods involve the use of expensive reagents, strongly acidic conditions and extended reaction times. In addition, some of these methods are limited to simple aliphatic ketones and are not applicable to aryl or sterically hindered ketones. Thus, there is still a need to develop a simple, convenient and efficient method for the cyanation of both aliphatic and aromatic ketones using inexpensive and readily available reagents. Owing to its unique catalytic properties, iodine has been extensively used as a catalyst for a plethora of organic transformations.[8] However, there are no examples of the cyanation of ketones with trimethylsilyl cyanide using molecular iodine as the catalyst.

In continuation of our interest on the catalytic applications of elemental iodine for various organic transformations,[9] we report herein a mild and convenient method for the cyanation of both cyclic and acyclic ketones with trimethylsilyl cyanide using elemental iodine as an efficient catalyst (Scheme 1).

The treatment of benzophenone with trimethylsilyl cyanide in the presence of 5 mol% of elemental iodine in dichloromethane afforded the corresponding trimethylsilylated cyanohydrin in 93% yield. Similarly, various ketones such as 2-phenyl-4-chromanone, acetophenone, α-methylcyclohexanone, tetralone, 2-acetylthiophene, and α-azido- and α-bromo-ketones



Scheme 1.

Keywords: ketones; trimethylsiyl cyanide; iodine; α-cyanohydrins.

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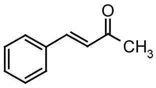
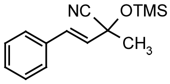
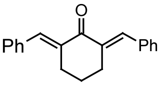
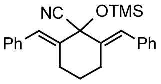
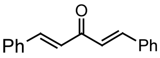
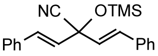
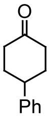
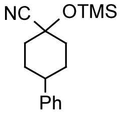
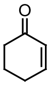
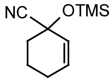
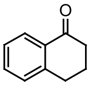
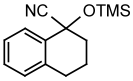
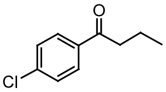
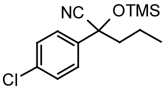
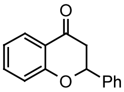
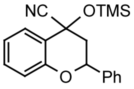
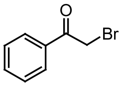
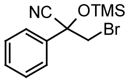
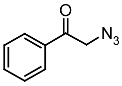
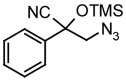
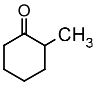
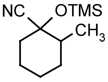
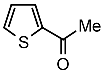
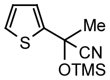
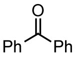
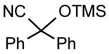
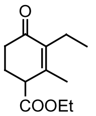
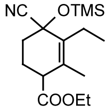
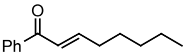
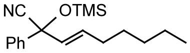
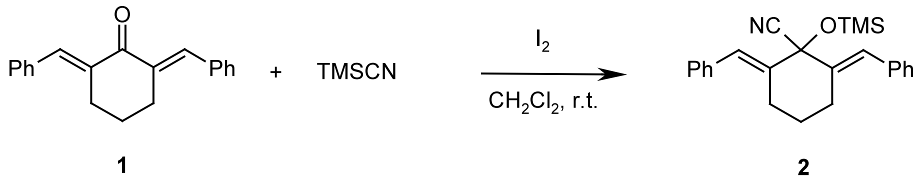
Table 1. Iodine-catalyzed preparation of cyanohydrin trimethylsilyl ethers

Entry	Ketone **1**	Product[a] **2**	Time (min)	Yield[b] (%)
a			20	90
b			30	85
c			25	87
d			35	89
e			25	88
f			35	90
g			25	92
h			20	89
i			35	90
j			20	87
k			30	89
l			20	91
m			25	93
n			30	82
o			40	85

a: All products were characterized by ^{1}H NMR, IR and mass spectroscopy
b: Isolated and unoptimized yields



Scheme 2.

were converted efficiently to the corresponding α-cyano silyl ethers using this procedure.[10] Enones such as 2-benzylidenecyclohexanone, 2-benzylidenecyclopentanone, 2-cyclohexen-1-one, benzylideneacetone, 4-phenyl-3-buten-2-one also reacted smoothly with trimethylsilyl cyanide in the presence of 5 mol% iodine to afford the corresponding 1,2-adducts in excellent yields (Scheme 2).

In case of α,β-unsaturated ketones, no 1,4-adduct was observed under these reaction conditions. In all cases, the reactions proceeded efficiently at ambient temperatures and were complete within 20–40 min. Dichloromethane is the solvent of choice giving the best results. This method is equally effective for the cyanation of both cyclic and acyclic ketones. The scope and generality of this process is illustrated with respect to various ketones including alkyl, aryl, and α,β-unsaturated ketones and the results are presented in Table 1. All products were characterized by ^{1}H NMR, IR, and mass spectroscopy and also by comparison with authentic compounds.[11] However, in the absence of a catalyst, the reaction did not yield any product even after a long reaction time. In most cases the yields are excellent, sometimes quantitative, making this method a useful synthetic protocol for the straightforward preparation of silylated cyanohydrins. Among catalysts such as CAN, DDQ, NBS, HI, IBX and $Mn(OAc)_3$, molecular iodine was found to be more efficient in terms of conversion and reaction time.

In summary, the paper describes a simple and efficient method for the cyanation of various functionalized and hindered ketones with TMSCN using the cheap and readily available elemental iodine as the catalyst. This method is effective for the cyanation of both aliphatic as well as aromatic ketones. In addition to its efficiency, operational simplicity and mild reaction conditions, this method provides high yields of products within a short time, which makes it a useful entry for the synthesis of trimethylsilyl ethers of cyanohydrins.

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10. *General procedure*: To a stirred solution of the ketone (1 mmol), and iodine (5 mol%) in dichloromethane (10 mL), TMSCN (1.2 mmol) was added slowly dropwise at 0°C and the mixtures were allowed to stir at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with dichloromethane (2×15 mL). The combined extracts were washed with 15% solution of sodium thiosulphate, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure trimethylsilyl derivative of the cyanohydrin.

    Spectral data for selected products **2b**: ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 9H), 1.85–2.05 (m, 2H), 2.10–2.25 (t, 4H, $J=6.8$ Hz), 7.0 (s, 2H), 7.25–7.50 (m, 10H). EIMS: m/z: 373 M^+, 358, 179, 115, 91, 73. IR (KBr) ν 3055, 3027, 2907, 2362, 1597, 1440, 1108, 967. **2f**: ^{1}H NMR (CDCl$_3$) δ: 0.20 (s, 9H), 1.85–2.05 (m, 2H), 2.10–2.25 (m, 2H), 2.75 (t, 2H, $J=6.8$ Hz), 6.95–7.05 (m, 1H), 7.10–7.25 (m, 2H), 7.45–7.58 (m, 1H). EIMS: *m*/*z*: 245 M$^+$, 203, 155, 129, 118, 84, 75, 45. IR (KBr) ν 3059, 2960, 2365, 1443, 1115, 1245, 857. **2h**: ^{1}H NMR (CDCl$_3$) δ 0.30 (s, 9H), 2.35–2.60 (dd, 2H, $J=7.0$, 12.5 Hz), 5.37 (dd, 1H, $J=1.0$, 12.5 Hz), 6.85 (d, 1H, $J=8.0$ Hz), 7.05 (t, 1H, $J=7.9$ Hz), 7.20–7.40 (m, 7H). EIMS: *m*/*z*: 323 M$^+$, 233, 204, 156, 141, 120, 73, 45. IR (KBr) ν 3035, 2965, 2335, 1443, 1245, 1120, 960, 763.

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