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ALKYL ISOCYANIDES AS PRECURSORS FOR THE FORMATION OF CARBON-CARBON BONDS

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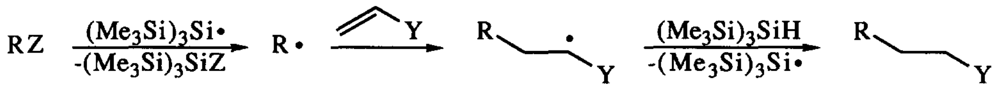
Summary: Tris(trimethylsilyl)silane is an effective mediator for the formation of carbon-carbon bonds via radicals using alkyl isocyanides as precursors.

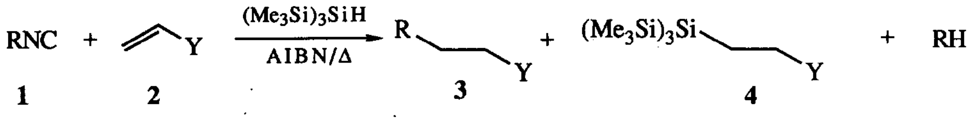
Free radicals are of considerable importance in the development of organic synthesis.[2] A very useful class of free radical reactions is the formation of carbon-carbon bonds either inter- or intramolecularly using iodides or bromides as starting materials.[3,4] These chain processes have often be accomplished using organotin and organomercury hydrides as mediators.[3,4] Recently we have found that $(Me_3Si)_3SiH$ can also be used as a mediator in the formation of C-C bonds, using iodides or bromides as precursors for alkyl radicals.[5] These processes occuring via radical chain reactions similar to tin method.



For a successful synthesis of this kind, it is important that (i) the $R_3M\cdot$ radicals react faster with the radical precursor than with the alkene, and (ii) the alkyl radical attacks alkene to form the adduct radical prior to reaction with the hydrogen donor. For example, carbon-carbon bond formation via radical addition to alkene does not take place when alkyl chlorides and isocyanides are used together with tributyltin hydride.[3] While the reason for the failure of alkyl chlorides is the low rate for chlorine abstraction by the tin radical,[6] for isocyanides the addition of stannyl radicals could also be slow or reversible.

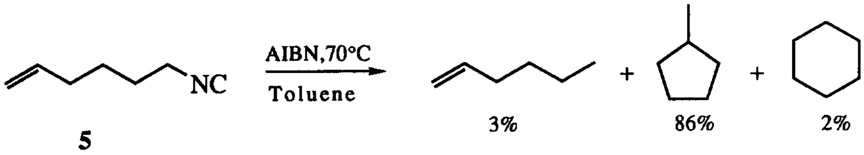
In our recent study on the tris(trimethylsilyl)silane[7] as radical-based reducing agents in syntheses, we found that the reduction of alkyl isocyanides is a facile process.[8] Furthermore $(Me_3Si)_3Si\cdot$ radicals add irreversibly to isocyanides with rate constant of ca. $5x10^7\ M^{-1}s^{-1}$.[7] Based on the above concept, we were persuaded that the C-C bond formation can take place when alkyl isocyanides are used together with $(Me_3Si)_3SiH$. The expectation turned out to be correct, and we here report our results on this new free radical process.

A solution of 4-5 mmol of alkyl isocyanide and 0.1 eq. of olefin in 40ml of toluene was placed in a two-necked round botton flask equipped with a magnetic stirring bar, argon inlet, reflux condenser and septum. A mixture of olefin (1.1 eq.), tris(trimethylsilyl)silane (1.2 eq.) and AIBN (7-8%) in 10 ml of toluene was added slowly (over 3-4 hours) via syringe pump. During the addition the solution was heated at 90°C. Heating was continued for 30 min. after the end of the addition. Evaporation and flash-chromatography (silica gel, pentane/ether) gave adducts **4** and **3**.[10] The overall reaction is shown below and the results are reported in Table 1.

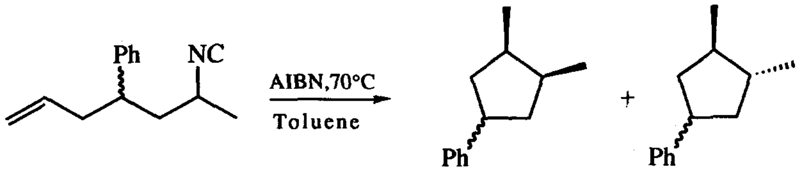


Compounds **4** are formed via radical addition of silane at the respective alkenes.[7,11] They can be easily separated from adducts **3** by flash chromatography. It is worth noting that the success of C-C bond formation depends upon the nucleophilicity of the alkyl radical. The more nucleophilic *tert*-alkyl radical leads to higher yields than *sec*- or *prim*-alkyl radicals in intermolecular addition reactions. With these radicals only alkenes with electron-withdrawing groups can be used.

Reaction of 5-hexenyl isocyanide[12] **5** with $(Me_3Si)_3SiH$ (0.05 M) in toluene at 70°C containing catalytic amounts of AIBN afforded the cyclized product in 88% yield (GC, using internal standard). Furthermore, the ratio of cyclized/uncyclized products is also in good agreement with the one obtained from the reduction of 5-hexenyl bromide by tris(trimethylsilyl)silane.[5]



Using this procedure for reaction of the secondary isocyanide **6**,[11] the desired cyclization products were isolated after workup in 78% yield as a 4.6:1 mixture of *cis* and *trans* isomers.

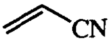
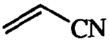
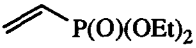
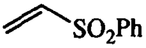
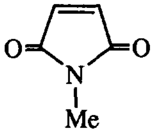
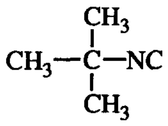
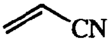
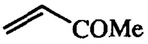


6

4.6:1 *cis/trans*, 78%

These experiments show that cyclization reactions with isonitriles give higher yields than the respective intermolecular C,C-bond forming reactions. This is because silyl radicals attack the electron rich olefinic bonds of isonitrile **5** and **6** about 10^2 times slower than the electron poor olefins of Table 1.[13] Therefore in cyclization reactions of **5** and **6** side products resulting from radical hydrosilylation are not observed.

Table 1. Radical-based reactions of alkyl isocyanides with olefins using tris-(trimethylsilyl)silane as mediator.

1	2	3 yield % (GC yield%)	4 yield % (GC yield%)
$CH_3(CH_3)_8CH_2NC$		36 (42)	32 (38)
		32 (37)	30 (35)
		54 (58)	20 (27)
		46 (51)	22 (29)
		48 (56)	26 (34)
		47 (58)	30 (34)
		37 (40)	55 (58)
 $(CH_3)_3C{-}NC$		54 (60)	22 (28)
		53 (59)	24 (29)
		48 (54)	35 (40)

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References and Notes

1. Visiting Scientist. Permanent address: I.Co.C.E.A., Consiglio Nazionale delle Ricerche, 40064 Ozzano Emilia (Bologna) Italy.
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6. The rate constants are in the range 10^3-10^4 $M^{-1}s^{-1}$ at room temperature (see: Ingold, K.U.; Lusztyk, J.; Scaiano, J.C. *J. Am. Chem. Soc.* **1984**, *106*, 343).
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8. The reduction yields of tertiary, secondary and primary isocyanides by Bu_3SnH are dependent on the temperature, i.e. the yields are good in boiling toluene or benzene for secondary and tertiary isocyanides, whereas primary isocyanides can be reduced in acceptable yields only in refluxing xylene with periodic additions of initiator.[9] Using $(Me_3Si)_3SiH$ this function can be replaced by hydrogen independently of the nature of the alkyl substituent at ca. 80°C.[7]
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10. Elementary analyses and spectroscopic data are in accored with the structures of all new compounds. Many of products **3** have already been described in: Giese, B.; Meister, J. *Chem. Ber.* **1977**, 110, 2588.
    Typical of silylated products **4** is a peak in the ^{1}H-NMR at $\delta = 0.19$ for the $(Me_3Si)_3Si$ group. MS shows successive loss of the Me_3Si group (m/z=73).
11. Kulicke, K.J.; Giese, B. *Synlett* **1990**, 91.
12. The alkyl isocyanides **5** and **6** were prepared by the following procedure:

$$ROH \xrightarrow{a} ROMs \xrightarrow{b} RN_3 \xrightarrow{c} RNH_2 \xrightarrow{d} RNHCHO \xrightarrow{e} RNC$$

a: MsCl, Pyr.; b: NaN_3; c: $LiAlH_4$; d: EtOCHO, p-TosOH, Et_3N; e: $POCl_3$, Et_3N.

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