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AN IMPROVED PROCEDURE FOR EFFICIENT GENERATION OF METHYL(OR p-TOLYL)THIOMETHYL GRIGNARD REAGENT AND ITS USE IN ORGANIC SYNTHESES

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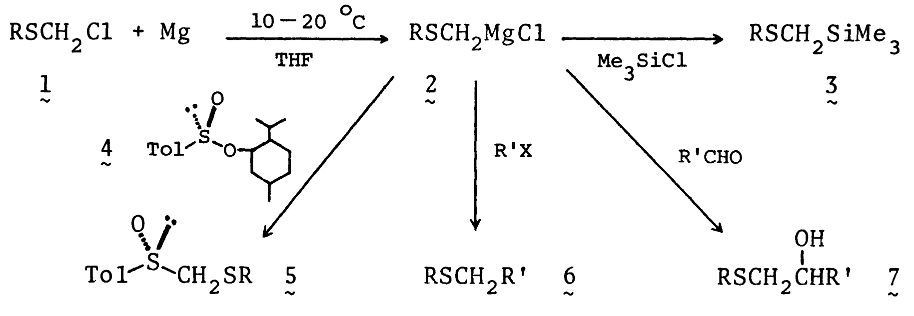
The optimal conditions for transformation of a chloromethyl sulfide into the corresponding Grignard reagent (2) in a high yield are established and 2 is shown to react with various functional groups such as an alkyl halide, an aldehyde, and a sulfinic ester, revealing its usefulness in organic syntheses.

It is well known that sulfenyl-substituted methyl carbanions are useful in organic syntheses,[1,2] and these carbanions were usually produced by the action of butyllithium on the corresponding methyl sulfides in the presence of N,N,N',N'-tetramethylethylenediamine or 1,4-diazabicyclo[2.2.2]octane.[3] Now, we wish to report an efficient preparation of methyl(or p-tolyl)thiomethylmagnesium chloride (2) and its utilization as an alternative source of the sulfenyl-stabilized carbanion for organic syntheses.

Hitherto, there have been two reports on successful formation of 2 ($R = CH_3$[4] or $PhCH_2$[5]) from the corresponding chloromethyl sulfide (1), but their yields are low[6] and insufficient for using 2 as a synthetic reagent. Furthermore, chloromethyl p-tolyl sulfide was reported to give only a coupling compound in the reaction with magnesium.[7] At the initial stage of our research, we made efforts to raise the yield of 2 in the reaction of 1 with magnesium. As a result of surveying the reaction conditions in detail, we have found that to keep the reaction temperature between 10 and 20 °C is important to efficient generation of 2. When the reaction was carried out above 20 °C, the coupling reaction occurred prior to formation of 2, and the reaction did not proceed at an appreciable rate below 10 °C. In a typical procedure, magnesium (0.6 g. atom), activated with a small amount of iodine and 1,2-dibromoethane, was suspended in tetrahydrofuran (THF) (200 ml) under a nitrogen atmosphere and then chloromethyl



a: $R = CH_3$
b: $R = p\text{-}CH_3C_6H_4$

[Tol ≡ $p\text{-}CH_3C_6H_4$]

methyl sulfide (0.29 mol) was added dropwise over a period of 1 h. During this period, the temperature of the reaction system was kept at 10–20 °C by cooling with ice-water and controlling the speed of dropping. After being stirred at room temperature for an additional hour, the solution of **2a** was obtained. The concentration of **2a** was determined by a titration method to be 1.30 mol/l which corresponded to 95% yield of **2a**. In a similar manner, **2b** was produced in 73% yield.

To illustrate the synthetic utility of **2** thus obtained, we investigated the reaction with *l*-menthyl p-toluenesulfinate (**4**), and **2** was found to be very useful reagent for making optically active formaldehyde dithioacetal S-oxide (**5**). The 1.30 mol/l solution (38 ml) of **2a** in THF was added to a THF solution of **4** (45.5 mmol) at 0 °C over a 15 min-period. After being stirred at 0 °C for 1.5 h, the usual work-up and chromatography on silica gel gave **5a** in 78% yield: $[\alpha]_D^{22}$ +278 (optical purity = 100%).8) Similar treatment of **4** with **2b** afforded **5b** in 81% yield: $[\alpha]_D^{22}$ +67.4 (o.p. = 88%).8) It is noteworthy that a sufficient amount of **2** in the present reaction is 1 mol-equiv to **4** in sharp contrast with the already reported method using methyl(or p-tolyl)thiomethyllithium and **4**, where 2 mol-equiv of the carbanion is required.2) Reaction of **2a** with dodecyl bromide in THF was accomplished by stirring at room temperature for 1 h and then at 50 °C for 2 h to produce methyl tridecyl sulfide (**6a**, R' = n-$C_{12}H_{25}$) in 76% yield. When **2a** was subjected to the reaction with benzaldehyde in THF, a smooth reaction took place at -78 °C for 80 min to afford an adduct (**7a**) in 71% yield. Furthermore, **2a** reacted with trimethylsilyl chloride in THF at room temperature for 12 h, and **3a** was obtained in 76% yield.

Thus it has been shown that methyl(or p-tolyl)thiomethyl Grignard reagent (**2**), derived efficiently from the easily available chloromethyl sulfide (**1**),7,10) can be employed instead of the sulfenyl-substituted methyllithium for organic syntheses.

References

1) I. Kuwajima, S. Sato, and Y. Kurata, Tetrahedron Lett., 1972, 737; R. L. Sowerby and R. M. Coates, J. Am. Chem. Soc., 94, 4758 (1972); J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. M. Coates, ibid., 95, 3429 (1973); T. Mukaiyama, Y. Watanabe, and M. Shiono, Chem. Lett., 1974, 1523; T. Shono, Y. Matsumura, S. Kashimura, and H. Kyutoku, Tetrahedron Lett., 1978, 2807; A. G. Schultz, W. Y. Lu, R. D. Lucci, B. G. Kurr, K. M. Lo, and M. Boxer, J. Am. Chem. Soc., 100, 2140 (1978); S. C. Welch and J.-P. Loh, J. Org. Chem., 46, 4072 (1981); A. P. Kozikowski and E. M. Huie, J. Am. Chem. Soc., 104, 2923 (1982).
2) L. Colombo, C. Gennari, and E. Narisano, Tetrahedron Lett., 1978, 3861.
3) E. J. Corey and D. Seebach, J. Org. Chem., 31, 4097 (1966); D. J. Peterson, ibid., 32, 1717 (1967).
4) H. Normant and B. Castro, C. R. Acad. Sci., 259, 830 (1964).
5) H. Sakurai, M. Kira, and M. Kumada, J. Chem. Soc. Chem. Commun., 1967, 889.
6) It was reported that reaction of **1a** with magnesium in THF at room temperature gave **2a**, which was directly trapped with trimethylsilyl chloride to give methyl trimethylsilylmethyl sulfide (**3a**) in 31% yield.5) Since **2a** was converted to **3a** in 76% yield as below mentioned, the yield of **2a** was estimated to be less than 47%.
7) F. G. Bordwell and B. M. Pitt, J. Am. Chem. Soc., 77, 572 (1955).
8) $[\alpha]_D^{22}$ +276 is the highest value already reported for (S)-**5a**,2) and $[\alpha]_D^{14}$ +76.8 for (S)-**5b**.9)
9) N. Kunieda, J. Nokami, and M. Kinoshita, Bull. Chem. Soc. Jpn., 49, 256 (1976).
10) Chloromethyl methyl sulfide (**1a**) is commercially available.

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