Pergamon

Tetrahedron Letters 40 (1999) 7055–7058

TETRAHEDRON
LETTERS

Reductive alkylation of α-cyano ketones induced by samarium iodide

Jia-Liang Zhu,[a] Kak-Shan Shia[b] and Hsing-Jang Liu[a,b,*]

[a]*Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2 Canada*
[b]*Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 300, China*

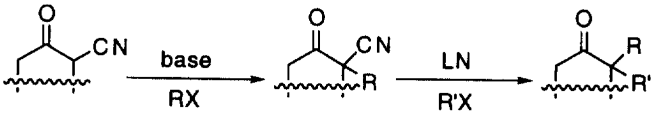
Received 19 May 1999; revised 16 July 1999; accepted 19 July 1999

Abstract

SmI_2–HMPA was shown to be an effective reagent for reductive alkylation of α-cyano ketones, a useful process for regiocontrol of α,α-dialkylation of ketones. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: samarium; samarium compounds; reduction; alkylation; cyano compounds.

Recently, we reported a convenient general procedure for regiocontrol of α,α-dialkylation of ketones.[1] The main thrust of this process is the reductive alkylation of an α-cyano ketone intermediate using lithium naphthalenide (LN) as a reducing agent (Eq. 1). In search of alternative reducing agents which might further enhance the synthetic utility of this process, samarium iodide,[2] which has been shown to be a useful reagent for reductive elimination of α-heterosubstituted (Br, Cl, SPh, SOPh, SO_2Ph, OAc, OTMS, OH, OCOBn, OTs, HgCl, etc.) ketones,[3] was explored. Although the use of this reagent alone was found to be ineffective, the combination of samarium iodide and hexamethylphosphoramide (HMPA) proved to be a viable alternative to LN in inducing reductive alkylation of α-cyano ketones, a process which promises to have broad synthetic utility.[4–7] Preliminary results are reported herein.



(1)

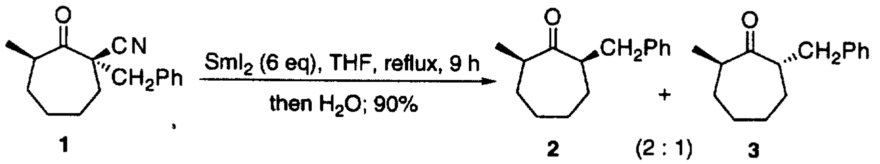
Our original investigation was carried out on cyano ketone **1** with samarium iodide in tetrahydrofuran.[8] At room temperature, the starting material was intact even after an extended period of 24 h. The reduction did occur at elevated temperature to give a 90% yield of ketones **2** and **3** in 2:1 ratio (Eq. 2). However, the reaction was fairly slow and it took about 9 h to complete. The long reaction time coupled with the high temperature required to induce the desired reductive decyanation made trapping of the ensuing enolate ion with an alkylating agent virtually impossible. This problem was circumvented with the addition of

---

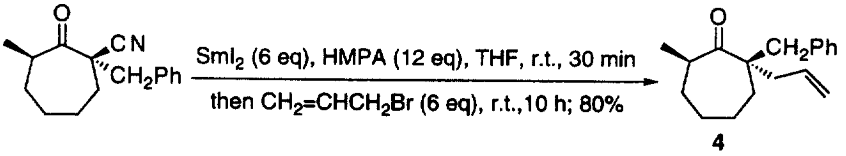
* Corresponding author.

PII: S0040-4039(99)01470-7

HMPA which is known to increase the redox potential of samarium iodide.[9,10] Thus, when cyano ketone **1** was treated with samarium iodide (6 equiv.)[11] in tetrahydrofuran in the presence of HMPA (12 equiv.)[10] at room tempature for 30 min followed by addition of allyl bromide (6 equiv.), the desired reductive alkylation product **4**[12] was obtained in 80% yield[13] after 10 h at room temperature (Eq. 3). This procedure was found to be general as shown by the results obtained for a number of selected α-cyano ketones compiled in Table 1. Alkylating agents examined include methyl iodide (entries 2 and 4), allyl bromide (entries 1, 3 and 5) and a 1° alkyl halide, 4-bromo-1-butene (entry 6). Aldehydes are apparently also suitable trapping agents. An example is found in entry 7. It is also noteworthy that in most of the cases examined, the alkylation was highly stereoselective giving rise to a single diastereomer (entries 1 and 3–6). When compared to the reductive alkylation using LN,[1] the current procedure is equally effective. The yields of products are quite comparable, although the alkylation step of the current procedure requires considerably longer time (1–14 h vs 1 h for most of the cases involving LN), apparently due to the lower reactivity of samarium enolates. Hence, samarium iodide represents itself as a viable alternative to LN to effect reductive alkylation of α-cyano ketones and expands the scope of synthetic utility of a newly developed process for regiocontrol of α,α-dialkylation of ketones, a frequently encountered synthetic practice for which few simple methods are available.[14–23]



(2)



(3)

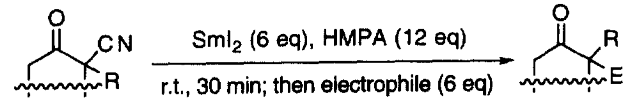
Acknowledgements

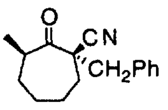
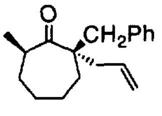
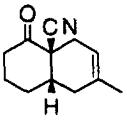
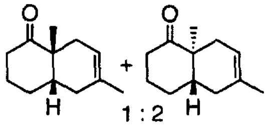
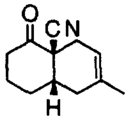
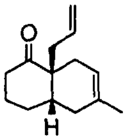
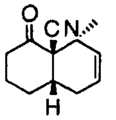
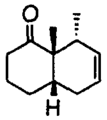
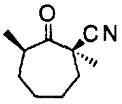
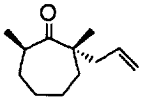
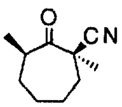
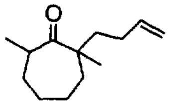
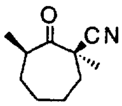
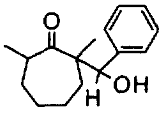
We are grateful to the Natural Sciences and Engineering Research Council of Canada and the National Science Council of the Republic of China for financial support.

References

1. Liu, H. J.; Zhu, J. L.; Shia, K. S. *Tetrahedron Lett.* **1998**, *39*, 4183–4186.
2. For a recent review, see: Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338.
3. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135–1138.
4. This process has been used recently as a key step[5] in an improved total synthesis of *cis*-clerodane diterpenoids.[6,7]
5. Yip, J. PhD Thesis, University of Alberta, 1998.
6. Liu, H. J.; Shia, K. S.; Han, Y.; Sun, D.; Wang, Y. *Can. J. Chem.* **1997**, *75*, 646–655.
7. Liu, H. J.; Shia, K. S. *Tetrahedron* **1998**, *54*, 13449–13458.
8. For preparation of samarium iodide as a stock solution, see: Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
9. Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485–1486.
10. Shabangi, M.; Flowers, R. A. *Tetrahedron Lett.* **1997**, *38*, 1137–1140.

Table 1
Reductive alkylation of α-cyano ketones with samarium iodide



Entry	α-Cyano Ketone	Time (h)	Electrophile	Product(s)	% Yield
1	 **1**	10	allyl bromide	 **4**	80
2		1	methyl iodide	 1 : 2	70
3		1.5	allyl bromide		60
4		2	methyl iodide		65
5		8	allyl bromide		75
6		15	4-bromo-1-butene	 [a]	60
7		8	benzaldehyde	 [b]	74

[a] A single diastereomer was formed. Its stereochemistry remains to be determined.

[b] Two diastereomers were formed in a ratio of 1 : 1.

11. The use of a less amount of the reagent often resulted in incompletion of the reaction under the specified conditions. The amount of the alkylating agent was adjusted accordingly to cover the expected side reactions with cyanide and with the excess samarium iodide, such as reductive dehalogenation.
12. The stereochemistry of this compound was confirmed by NOE experiments. Results are compiled in Fig. 1. Where applicable, the stereochemistry of other products listed in Table 1 was also deduced in a similar fashion.
13. Yields are for purified products and unoptimized.
14. House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin: New York, 1972; 2nd ed.; pp. 492–628.
15. Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615–1619.

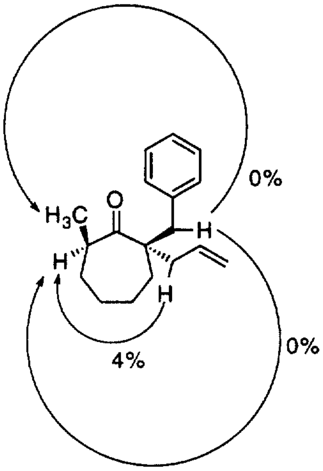


Figure 1.

16. Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1620–1627.
17. Boatman, S.; Harris, T. M.; Hauser, C. R. *J. Am. Chem. Soc.* **1965**, *87*, 82–86.
18. Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275–286.
19. Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 1027–1029.
20. Coates, R. M. *Angew. Chem., Int. Ed. Engl.* **1973**, 586.
21. Kamata, S.; Uyeo, S.; Haga, N.; Nagata, W. *Synth. Commun.* **1973**, *3*, 265–272.
22. Nedelec, L.; Gasc, J. C.; Bucourt, R. *Tetrahedron* **1974**, *30*, 3263–3268.
23. Saito, S.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 611–612.