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Unusual radical *ipso*-substitution reaction of an aromatic methoxy group induced by tris(trimethylsilyl)silane-AIBN or SmI_2

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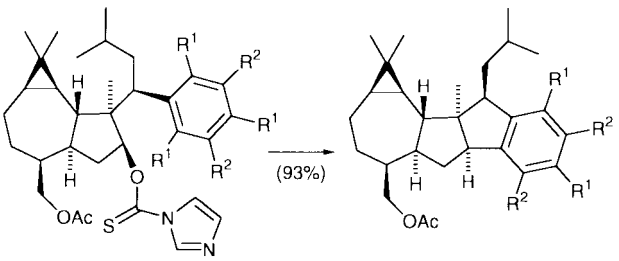
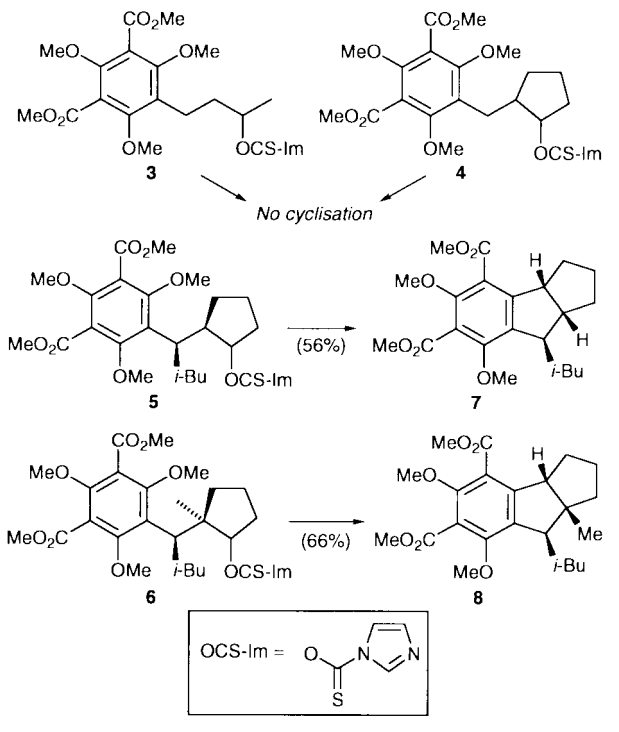
While conformationally favourable thiocarbamates bearing an aromatic methoxy group undergo intramolecular *ipso*-substitution of the methoxy group by treatment with tris(trimethylsilyl)silane (TTMSS) and AIBN, either conformationally flexible or favourable ketones easily cyclise into a five- or six-membered rings by treatment with SmI_2.

Radical cyclisation is one of the most useful methodologies for formation of a wide variety of carbon skeletons.[1] Particularly, the intramolecular reaction of the radical with an aryl group would provide an efficient synthetic route for constructing polycyclic systems containing an aromatic ring. During the course of our program directed toward the synthesis of macrocarpals,[2] we observed an unusual *ipso*-substitution of an aromatic methoxy group by treatment of the thiocarbamate **1** with TTMSS[3] and AIBN, yielding a cyclised product **2** (Scheme 1). A search of the literature revealed that there is no report describing the successful radical aromatic *ipso*-substitution of a methoxy group.[4] Accordingly, we undertook an investigation to identify the essential factor for the progress of this unusual cyclisation.[5]

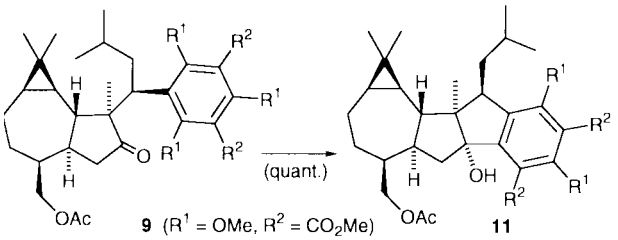
First, we prepared racemic thiocarbamates **3**–**6** bearing the substituted phenyl group, and exposed them to the radical cyclisation conditions described above. As shown in Scheme 2,

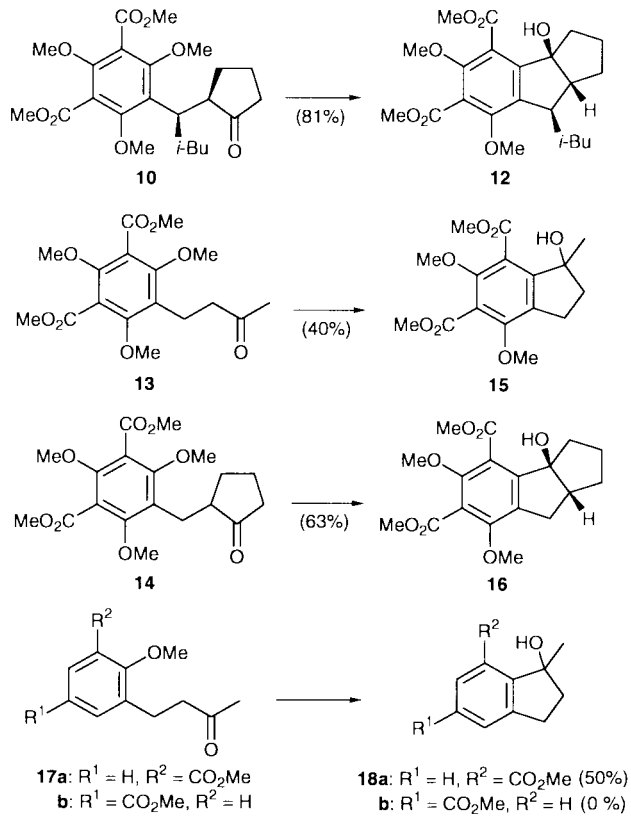


Scheme 1



Scheme 2





Scheme 3

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we observed no cyclisation by treatment of **3** or **4** with TTMSS–AIBN. However, conformationally more restricted thiocarbamates **5** and **6** gave the desired cyclised products **7** and **8**, respectively. In sharp contrast, the respective epimers of **5** and **6** at the benzylic position led to undesired reduction (deoxygenation or removal of thiocarbamate) under identical reaction conditions.

Based on these results, it is apparent that TTMSS-induced *ipso*-substitution is highly dependent on the steric nature of the starting thiocarbamates. Although the ground state and the reactive conformer are not necessarily the same, the conformation of radical intermediates, because of their low activation energy, is understood to have a significant effect on the course of the reaction. According to calculations,[6] the location of the alkyl radical generated from **5** and **6** is close to the reaction site (3.46 and 3.49 Å, respectively) in the most stable conformer.

This novel cyclisation is expected to be applicable to a wide range of substrates if the distance between the radical and aryl methoxy group could be shortened in some way. We then turned our attention to the strong chelating ability of samarium.[7] Since no information was available as to whether the aromatic methoxy group could be appropriately replaced by a ketyl radical, we initially explored SmI_2-induced cyclisation of the conformationally favoured ketones **9** and **10**. As shown in Scheme 3, these ketones were treated with 3.5 equivalents of SmI_2 in THF at room temperature, affording cyclised products **11** and **12**, respectively. Next, it was found that sterically more flexible ketones **13** and **14** could also be cyclised into **15** and **16** by exposure to SmI_2, as we expected. It should be clearly noted that in the TTMSS-induced reaction, we could obtain no cyclised products using the thiocarbamates **3** or **4** derived from the ketones **13** and **14** (Scheme 2). Interestingly, while **17a** gave the cyclised product **18a** in 50% yield, the ketone **17b** led to recovery of the unchanged starting material (64%) along with isolation of a small amount of the alcohol as a reduction product (22%).

Based on these observations, we propose the mechanism of chelation-induced cyclisation, as shown in Fig. 1. The ketyl radical intermediate **A**, generated by the reaction of the ketone **17a** with SmI_2, would be folded like **B** by the chelation of Sm(III) with the oxygen of both the methoxy and the ester group. Such chelation might attract the ketyl radical close to the reaction site, which enables the ketyl radical to attack the aromatic carbon. The resulting dienyl radical **C** was then reduced to the anionic species **D** by single electron transfer by SmI_2, followed by elimination of methoxide and hydrolysis to give **18a**.

In conclusion, we have developed a novel cyclisation reaction by radical *ipso*-substitution of an aromatic methoxy group. While TTMSS-induced cyclisation is highly dependent on the structure of the starting materials, SmI_2-mediated cyclisation was found to be applicable to conformationally flexible substrates. The scope and limitation of this novel cyclisation, and application to the synthesis of natural products are now being investigated in this laboratory.

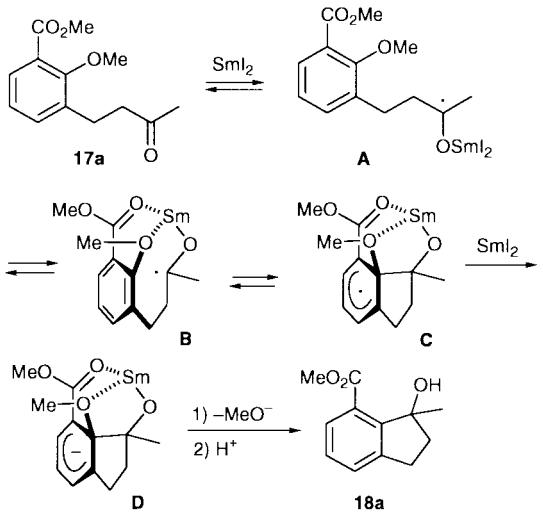

Fig. 1

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Notes and references

1 B. Giese, in *Organic Chemistry Series, Vol. 5, Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, ed. J. E. Baldwin, Pergamon, Oxford, 1986, pp. 141–266; D. P. Curran, in *Comprehensive Organic Synthesis, Vol. 4*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, pp. 779; P. A. Baguley and J. C. Walton, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 3072; A. Krief and A.-M. Laval, *Chem. Rev.*, 1999, **99**, 745; W. R. Bowman, C. F. Bridge and P. Brookes, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1.

2 T. Tanaka, H. Mikamiyama, K. Maeda, T. Ishida, Y. In and C. Iwata, *Chem. Commun.*, 1997, 2401; T. Tanaka, H. Mikamiyama, K. Maeda and C. Iwata, *J. Org. Chem.*, 1998, **63**, 9782.

3 M. Ballestri, C. Chatgilialoglu, K. B. Clark, D. Griller, B. Giese and B. Kopping, *J. Org. Chem.*, 1991, **56**, 678.

4 Demethoxylative C–C bond formation is known to occur in very limited cases, see: W. S. Lee, I.-Y. Jeong, M. Shiro, S. Sano and Y. Nagao, *Tetrahedron Lett.*, 1997, **38**, 611; R. Yanada, N. Negoro, M. Okaniwa, Y. Miwa, T. Taga, K. Yanada and T. Fujita, *Synlett*, 1999, 537; for C–O bond formation, see: K. Nowada, H. Sakuragi, K. Tokumaru and M. Yoshida, *Chem. Lett.*, 1976, 1243.

5 For related works, see: H.-G. Schmalz, S. Siegel and J. W. Bats, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2383; O. Hoffmann and H.-G. Schmalz, *Synlett*, 1998, 1426; C. U. Dinesh and H.-U. Reissig, *Angew. Chem., Int. Ed.*, 1999, **38**, 789; D. Crich and J.-T. Hwang, *J. Org. Chem.*, 1998, **63**, 2765; J. Boivin, M. Yousfi and S. Z. Zard, *Tetrahedron Lett.*, 1997, **38**, 5988; A. Citterio, R. Sebastiano, A. Maronati, R. Santi and F. Bergamini, *J. Chem. Soc., Chem. Commun.*, 1994, 1517.

6 MD and MO calculations were performed by SPARTAN (Ver. 5.1.1) using MM 2 method and PM 3 Hamiltonian.

7 P. Girard, J. L. Namy and H. B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693; G. A. Molander, *Chem. Rev.*, 1992, **92**, 29; G. A. Molander and C. R. Harris, *Chem. Rev.*, 1996, **96**, 307; A. Krief and A.-M. Laval, *Chem. Rev.*, 1999, **99**, 745.