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SmI_2-Mediated Carbon−Carbon Bond Fragmentation in α-Aminomethyl Malonates

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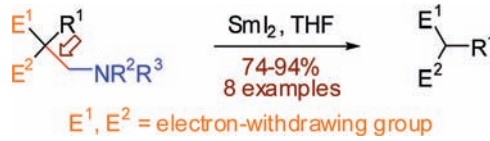
ABSTRACT



A new and efficient samarium diiodide-promoted carbon−carbon bond fragmentation reaction of α-aminomethyl malonates, taking place normally at room temperature and generating the corresponding deaminomethylation products in 74−94% yields, is reported. The presence of the amino group is necessary for the success of the current transformation.

Samarium diiodide, or SmI_2, was first introduced by Kagan in the late 1970s as a powerful one-electron reducing agent for a variety of organic functional groups.[1] Since then, it has been extensively employed to mediate many processes ranging from functional group interconversion to complex carbon−carbon bond-forming sequences.[2] Among those transformations, a number of fragmentation reactions have been investigated, the majority of which have been aimed at carbon−heteroatom bond fragmentation such as dehalogenation, deoxygenation, and deamination.[2k,3] In contrast, relatively few endeavors have been devoted to the carbon−carbon bond fragmentation reactions although they just started to gain increasing popularity in recent years.[4] For the latter category, the presence of a ring-strained system[5] or a leaving group[6] (such as halo atoms, dithiocarbonyl group, etc.) is usually required to trigger the reaction, while certain 1,4-diketones,

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(3) For a comprehensive account of carbon−heteroatom bond fragmentation, see: (a) Concellon, J. M.; Rodriguez-Solla, H. *Eur. J. Org. Chem.* **2006**, *7*, 1613. (b) Dahlen, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. For some recent work, see: (c) Honda, T.; Hisa, C. *Tetrahedron Lett.* **2009**, *50*, 4654. (d) Lam, K.; Marko, I. E. *Org. Lett.* **2009**, *11*, 2752. (e) Honda, T.; Aranishi, E.; Kaneda, K. *Org. Lett.* **2009**, *11*, 1857. (f) Wang, X.; Mao, H.; Xie, G.; Du, J. *Synth. Commun.* **2008**, *38*, 2908. (g) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660. (h) Enholm, E. J.; Schreier, J. A. *J. Org. Chem.* **1995**, *60*, 1110.

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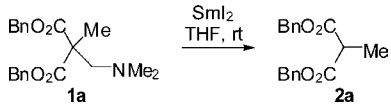
within either ring-strained or strain-free systems, have been found to undergo carbon−carbon bond fragmentation.[7]

Recently, we investigated the reaction of SmI_2 with a series of α-aminomethyl malonates, a type of strain-free substrate containing a quaternary carbon center adjacent to the alkoxycarbonyl groups. Upon treatment with freshly prepared SmI_2 (1.1 equiv), approximately 50% of diester **1a** was converted into **2a** within 20 min (Table 1, entry 1), through

Table 1. Optimization of Reaction Conditions with **1a**



1a **2a**

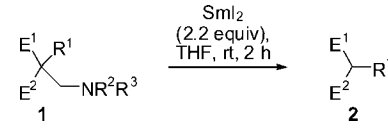
entry	SmI_2 (equiv)	time	yield[a] (%)
1	1.1	20 min[b]	ca. 50[c]
2	2.0	20 min[b]	88
3	2.2	2 h	94
4	5.0	2 h	87

[a] Isolated yield. [b] The reaction mixture turned from blue to yellow after about 20 min, indicating that SmI_2 was completely consumed. [c] Estimated yield based on a TLC analysis.

a new and intriguing type of carbon−carbon bond fragmentation. If the quantity of SmI_2 was increased to 2.0 equiv, the reaction was complete in 20 min, affording **2a** in 88% yield (entry 2). When the substrate was treated with more SmI_2 (2.2 and 5.0 equiv) for longer reaction time (2 h), the yields were found to be 94% and 87%, respectively (entries 3 and 4). Therefore, the quantity of SmI_2 and the reaction time were fixed at 2.2 equiv and 2 h, respectively, for most of the subsequent experiments.

To examine the generality and scope of the SmI_2-mediated carbon−carbon bond fragmentation method, a series of α-aminomethyl malonates[8] were scrutinized (Table 2). The following observations have been made. (i) The R^1 group in **1** (Table 2) can be a methyl, a benzyl, or a methylene within a lactone ring. (ii) Except for **1f** and **1i**, all malonate

Table 2. SmI_2-Mediated Carbon−Carbon Bond Fragmentation of **1**



1 **2**

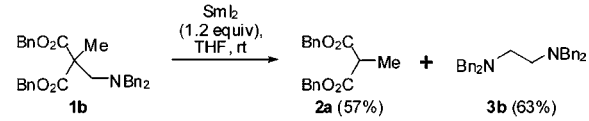
entry	substrate	yield[a] (%)
1	**1a**: R = Me	94
2	**1b**: R = Bn	94
3	**1c**: R, R = $(CH_2)_5$	89
4	**1d**: R = Me	90
5	**1e**: R, R = $(CH_2)_2O(CH_2)_2$	85
6	**1f**: "NR_2" = "$N^+Me_3I^-$"	0
7	**1g**: R = R' = Et	77
8	**1h**: R = Ph, R' = H	74[b]
9	**1i**: R = Ph, R' = Ac	0
10	**1j**	94

[a] Isolated yield. [b] SmI_2 (5 equiv) was added while the substrate was heated in THF, and the mixture was then heated at reflux for an additional 0.5 h.

derivatives (dibenzyl, dimethyl, or diethyl malonates, or a lactone) underwent clean and smooth fragmentation to form the corresponding products in good to excellent yields (74−94%, entries 1−5, 7, 8, and 10). (iii) The presence of the amino group is necessary for the success of the reaction. For example, it can be a dimethylamino, diethylamino, dibenzylamino, piperidinyl, morpholinyl, or anilino group. No reaction occurred in the case of amide **1i** (entry 9), and a messy mixture was generated from ammonium **1f** (entry 6). In addition, as demonstrated by further studies, replacement of the amino group with an iodo, ethoxy, or phenyl did not bring about the desired fragmentation. (iv) While tertiary amine substrates reacted readily at room temperature, a secondary amine counterpart **1h** (entry 8) required both harsher reaction conditions and extra SmI_2 to secure a useful transformation.

The current fragmentation seems to proceed via a free radical reaction pathway. To collect pertinent evidence, the following experiment was executed. As shown in Scheme 1,

Scheme 1. Reaction of **1b** with 1.2 Equiv of SmI_2



1b **2a** (57%) **3b** (63%)

careful addition of SmI_2 (1.2 equiv) to a solution of compound **1b** in THF did provide the homocoupling product **3b** (63%) in addition to the fragmentation product **2a** (57%). Successful isolation of dimer **3b** has thus confirmed our hypothesis that the reaction involves free radical intermediates.

(5) For examples of SmI_2-promoted C−C bond in ring-strain systems, see: (a) Lange, G. L.; Gottardo, C.; Merica, A. *J. Org. Chem.* **1999**, *64*, 6738. (b) Lange, G. L.; Merica, A. *Tetrahedron Lett.* **1999**, *40*, 7897. (c) Lange, G. L.; Furlan, L.; MacKinnon, M. C. *Tetrahedron Lett.* **1998**, *39*, 5489. (d) Lange, G. L.; Gottardo, C. *Tetrahedron Lett.* **1994**, *35*, 6607. (e) Comins, D. L.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1994**, 2681. (f) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112. (g) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6649. (h) Beerli, R.; Bruner, E. J.; Broschberg, H. J. *Tetrahedron Lett.* **1992**, *33*, 6449. (i) Hwang, J. T.; Liao, C. C. *Tetrahedron Lett.* **1991**, *32*, 6583.

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(8) Compounds **1a**−**g** and **1j** were prepared according to: (a) Miller, R. B.; Smith, B. F. *Synth. Commun.* **1973**, *3*, 359. Compound **1h** was prepared according to: (b) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aube, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226. The detailed preparation for these compounds can also be found in the Supporting Information.

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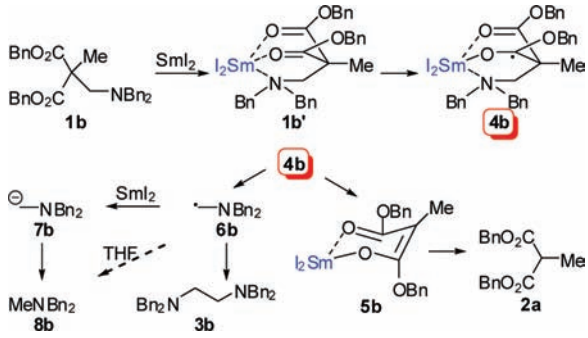
On the basis of all the information described above, a tentative mechanism has been proposed for the fragmentation reaction of α-aminomethyl malonates (Scheme 2). Com-

Scheme 2. Proposed Mechanism



pound **1b** is taken as an example here to illustrate the reaction pathways. Upon treatment with SmI_2, simultaneous coordination[9,10] of samarium to an electron-rich nitrogen atom and two carbonyl oxygen atoms might take place to form **1b′**. Unsuccessful transformation of **1f** and **1i** presumably resulted from failure in prior tridentate coordination to samarium. Subsequently, partial reduction of **1b′** is realized through single electron transfer (SET) to produce a ketyl radical anion **4b**, in which Sm(III) might also coordinate to the nitrogen and the carbonyl oxygen of the other ester group. Fragmentation of **4b** leads to Sm(III) enolate **5b** and radical **6b**. Primary radical **6b** can either undergo dimerization via homocoupling to give **3b** or be further reduced to afford anion **7b** in the presence of excess SmI_2. After aqueous workup, **5b** and **7b** are transformed into **2a** and **8b**, respectively. Alternatively, radical **6b** could attract a proton from the solvent to afford **8b**.[11]

In conclusion, we have developed a novel and efficient SmI_2-promoted carbon−carbon bond fragmentation reaction of α-aminomethyl malonates, which takes place normally at room temperature and generates the deaminomethylation products in 74−94% yields. The presence of the amino group is necessary for the success of the transformation. The current fragmentation can be considered conceptually as a retro-Mannich reaction (although no aldehydes or imines would be obtained from this reaction), which should find potential applications in organic synthesis.

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Supporting Information Available: Experimental procedures, analytical data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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