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Synthesis of Succinic Diesters via Reductive Coupling of α-Haloesters Using Samarium (II) Iodide and HMPA

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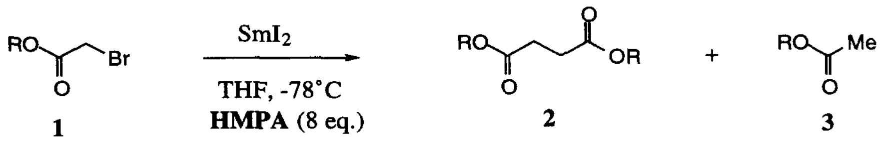
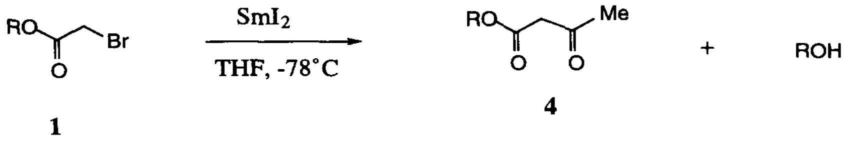
Abstract: *Primary and secondary α-haloesters are converted to succinic diesters in good yield by treatment with SmI_2-HMPA.*

Succinic acids may be obtained by oxidative coupling of dilithiated carboxylic acids as shown first by Ivanoff[1] and subsequently by other groups.[2] Renaud and Fox have unambiguously shown that the mechanism of this reaction involves a radical intermediate.[3] The dimerization reaction also proceeds to a lesser extent with ester[4] and ketone enolates.[5]

We now wish to report that samarium (II) iodide, in the presence of hexamethylphosphoramide (HMPA), promotes the reductive coupling of α-bromoacetates to succinic acid diesters (equation 1). The result is in clear contrast to that of Kim *et al.* who recently reported that α-bromoacetates reacted with samarium (II) iodide to provide β-ketoesters (equation 2).[6] Furthermore, several related Reformatsky-type addition reactions of bromoacetates have also been reported,[7] but to our knowledge, there are no reports on the dimerization of α-bromoacetates. Table 1 shows the results obtained with primary bromoacetates in the presence of HMPA. Succinic diester **2a**[8] was formed in low 18% isolated yield (entry a) along with 58 % of the reduction product



(equation 1)

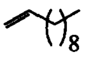
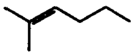
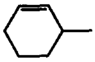
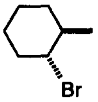


(equation 2)[ref 6]

3a when bromoacetate **1a** was added to SmI_2 (2 eq.) and HMPA (8 eq.) in THF at -78°C (Method A). Conversely, when 2.5 eq. of SmI_2 was added to a solution of **1a** in THF and HMPA (8 eq.) at -78°C (Method B), the isolated yield of **2a** increased to 34% and the acetate **3a** was also formed in 43% yield.

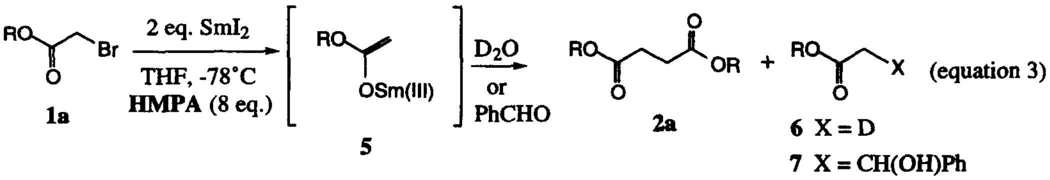
Table 1. Yields of Succinic Diesters 2 and Acetates 3 by Dimerization of α-Bromoacetates with SmI_2-HMPA

Method : A : additon of **1**/ THF to SmI_2 (2 eq.) + HMPA (8 eq.)
B : SmI_2 (2.5 eq.) added to **1**/ THF + HMPA (8 eq.)
C : i) SmI_2 (2.1 eq.) added to **1**/ THF + HMPA (8 eq.) ii) addition of **1** (1 eq.)/ THF

Entry	R	Method	Yield[a] (%): **2**	**3**
a		A	18	58
		B	34	43
		C	59 (83)[b]	3
b		C	61 (81)[b]	--[c]
c		A	16	48
		C	51 (74)[b]	9
d		A	56[d] (80)[b]	8

[a] Unless otherwise specified all yields refer to isolated yield. [b] corrected yield based on recovered **1**, see text.
[c] Not quantified,volatile compound. [d] (1:1) mixture of diastereoisomers.

While we were trying to identify the source of the reduction product, hints towards optimizing reaction conditions came from the following observation. When only 0.5 eq. of SmI_2 was added to a solution of **1a** in THF containing HMPA (8 eq.) at -78 °C, succinic diester **2a** (20% isolated, 74% based on recovered **1a**) and trace of the reduction product **3a** were isolated. This seemed to indicate that the acetate product **3a** of the reactions described in Methods A and B came from protonation of unreacted samarium (III) enolate **5** (equation 3). In fact, when D_2O or benzaldehyde were used as electrophile prior to aqueous work-up procedures (under



the reaction conditions described for Method A), deuterated acetate **6** and β-hydroxyester **7** were formed in 55% (40% deuterium incorporation) and 61% yield respectively. When treated with SmI_2-HMPA, bromoacetate **1a** therefore afforded a mixture of samarium enolate **5** and diester **2a** and, consequently, optimal conversion to the latter required adding more bromoacetate **1a** to the reaction mixture. Indeed, when 1 eq. of bromoacetate **1a** was added before quenching the reaction (Method C),[9,10] diester **2a** was isolated in 59% yield (83% based on recovered **1a**) along with only 3% of acetate **3a**. We have duplicated the reaction reported by Kim and co-workers[6] using the bromoacetate derived from cyclohexenol (**1c**) and obtained similar results. When carried out with 8 eq. of HMPA at -78 °C, the reaction afforded **2c** in 74% yield. It should be pointed out that none of the Claisen-type products (e.g. **4**) were observed in this and other reactions described in Tables 1 and 2.

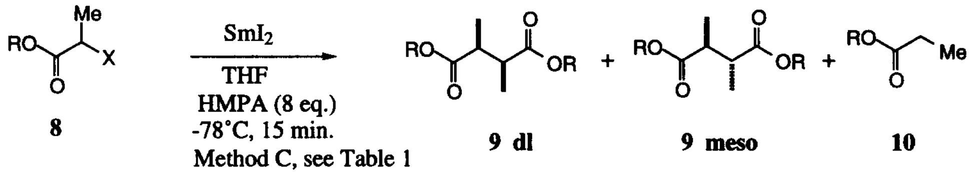
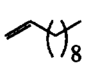
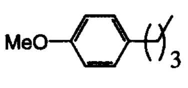


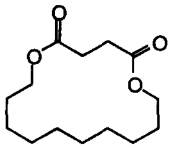
Table 2. Yields of 2,3-Dimethylsuccinic Diesters 9 and Propanoates 10 by Dimerization of α-Halopropanoates with SmI_2-HMPA

Entry	R	X	Yield^a (%):	9 dl	9 meso	10
a		Br		56	14	8
b		I		53	16	10
c		Br		48	19	7
d		I		46	22	9

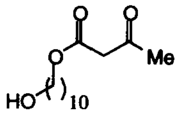
[a] Isolated yields (corrected based on recovered **8**, see Method C, Table 1).

α-Bromopropanoates also react with SmI_2-HMPA to afford 2,3-dimethylsuccinic diesters in good yield (Table 2). Bromopropanoates **8a** and **8c** and iodopropanoates **8b** and **8d** afforded mixtures of **9** ***dl*** and **9** ***meso*** isomers.[11] The reactivity of tertiary bromoesters was also studied. The bromoisobutyrate analog of **8c** failed to dimerize with SmI_2-HMPA and the corresponding isobutyrate was the only product obtained in almost quantitative yield. Similarly, several other tertiary bromides tested gave only reduction products. This revealed one of the limitations of this method and, along with the results related to equation 3, ruled out the possibility of a radical-type coupling mechanism.[2,3]

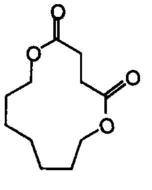
Finally, we studied the intramolecular cyclization of *bis*-bromoacetates. The *bis*-bromoacetate derived from 1,10-decanediol was treated with SmI_2-HMPA to afford the 16-membered ring dilactone **11**[12] in 19% iso-



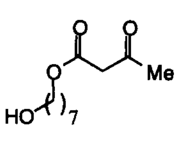
11 (19%)



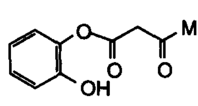
12 (16%)



13 (22%)



14 (19%)



15 (20%)

lated yield. Contrary to the intermolecular reactions, the Claisen-type condensation product **12** was also isolated in 16% yield. The same reactivity pattern was observed for the *bis*-bromoacetate derived from 1,7-heptanediol as dilactone **13**[12] and β-ketoester **14** were formed in equimolar quantity. The *bis*-bromoacetate derived from ethylene glycol gave none of the corresponding 8 membered-ring dilactone [13] and the more rigid catechol *bis*-bromoacetate gave only β-ketoester **15** in 20% yield.

In summary, the addition of HMPA to SmI_2 promoted the formation of succinic diesters from α-haloesters and, with the exception of intramolecular reactions, the previously reported β-ketoester products[6] were not observed under these conditions.

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References and Footnotes

1. Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76.
2. a) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969; b) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549; c) idem. *ibid* **1988**, *53*, 4724; d) Langer, T.; Illich, M.; Helmchen, G. *Tetrahedron Lett.* **1995**, *36*, 4409; e) Porter, N. A.; Su, Q.; Jill, J. H.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457.
3. Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745.
4. a) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521; b) Babler, J. H.; Sarussi, S. J. *J. Org. Chem.* **1987**, *52*, 3462.
5. Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487.
6. Park, H. S.; Lee, I. S.; Kim, Y. H. *Tetrahedron Lett.* **1995**, *36*, 1673.
7. a) Molander, G. A.; Etter, J.B. *J. Am. Chem. Soc.* **1987**, *109*, 6556; b) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291; c) Moriya, T.; Handa, Y.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29*, 6947.
8. All new compounds reported here gave satisfactory ^{1}H and ^{13}C NMR, MS and combustion analyses.
9. **Typical procedure**: (*Gas-tight syringes should be used*). Under argon, a (0.1M, Aldrich) solution of samarium iodide (14.7 mL) was added dropwise at -78°C to a degassed solution of bromoacetate **1a** (194 mg, 0.7 mmol) and HMPA (975 μL, 5.6 mmol) in THF (3 mL). The mixture was stirred at -78 °C for 15 minutes and a solution of **1a** (194 mg, 0.7 mmol) in THF (600 μL) was added. The mixture was stirred at -78°C for 30 minutes and a solution of 5% $NaHCO_3$ (25 mL) and (1: 5) Et_2O-hexane (25 mL) were added. The separated aqueous layer was extracted with (1: 5) Et_2O-hexane (2 x 25 mL) and the combined organic layers were washed (brine), dried ($MgSO_4$ anh.), filtered and evaporated. Flash-chromatography (EtOAc-hexane (1: 20)) of the residue gave **2a** (162 mg, 59%) along with **1a** (114 mg).
10. Before quenching the reaction, adding bromoacetate **1a** to the mixture (step ii, Method C) in molar quantity equivalent to that of **5** (ca. 60% Method A and 40% Method B) did not result in a complete conversion **1a** to **2a**. Because the polarity of compounds **1**,**2** and **3** is similar, adding benzaldehyde (see **5** → **7**) before work-up represents a practical alternative to sometimes difficult chromatographic separations.
11. The structure of *meso* and *dl* isomers reported in Table 2 were correlated with the products obtained by esterification of commercially available *meso* and *dl* 2,3-dimethylsuccinic acid (DBU, RI, CH_3CN).
12. Spanagel, E. W.; Carothers, W. H. *J. Am. Chem. Soc.* **1935**, *57*, 929.
13. The synthesis of 8 membered-ring dilactone has been reported: Lee, E.; Lee, D. S.; Lee, K. H.; Choi, I. S. *Bull. Korean Chem. Soc.* **1992**, *13*, 470.

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