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Communication

SmI_2 Mediated Reaction of *N*-(Haloalkyl)-*N*-phenylformamide: Homologation

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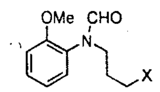
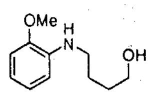
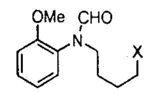
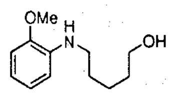
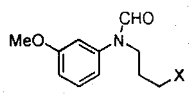
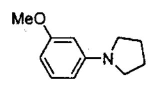
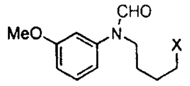
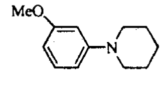
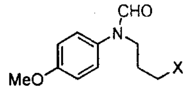
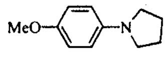
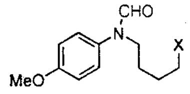
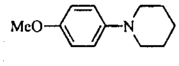
Since Kagan's report about reactions using samarium diiodide in 1980,[1] samarium Barbier reaction has been an important and popular method to couple alkyl halides and carbonyl compounds, such as aldehydes, ketones and esters. In particular, intramolecular Barbier reaction has been developed into a powerful synthetic tool by Molander[2] and others.[3]

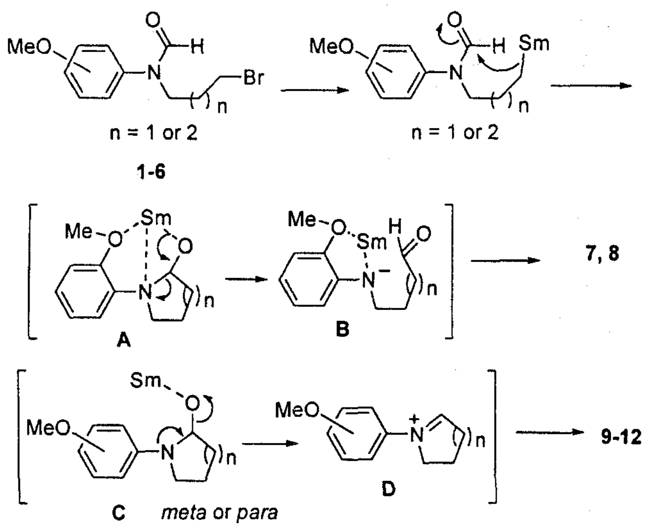
Several kinds of samarium diiodide promoted reactions of amides have been reported. Aromatic carboxamides are reduced to benzyl alcohols under basic conditions[4a] and to benzaldehydes under acidic conditions[4b] using 4 equiv. of SmI_2. The coupling of amides utilizing SmI_2/Sm in THF has been reported to result in the formation of vicinal diaminoalkenes *via* carbene intermediates.[5] The intramolecular Barbier reaction of imides with SmI_2 and HMPA in THF at −78 °C has also been known to give alcohols.[6] An intramolecular nucleophilic acyl substitution reaction of halo-substituted amide to a ketone at −78 °C has been reported.[7] However, the samarium mediated Barbier type reaction of amides is unknown as far as we know.

We report here our preliminary results that *N*-haloalkylformamides reacted with SmI_2 in the presence of HMPA at −78 °C in THF to give two types of products depending on the position of a methoxy substituent: cyclized products (**9-12**) and one carbon homologated alcohol (**7** and **8**). All of the *N*-bromoalkylformamides (**1a-6a**) or *N*-iodoalkylformamides (**1b-6b**) were prepared by the known methods.[8] Under the reaction condition,[9] the reaction of the substrates with a methoxy group at the *ortho* position (**1a, 2a**) gave the one carbon homologated alcohols **7** and **8** respectively as shown in Table 1, while *N*-bromoalkylformamides with a methoxy group at the *meta* or *para* position (**3a-6a**) gave the heterocyclic pyrrolidines (**9** and **11**) or piperidines (**10** and **12**), respectively. The yields of the amides substituted with a methoxy group at the *ortho* and *para* position (**1, 2, 5** and **6**) are generally higher than those of the amide with a methoxy group at the *meta* position (**3, 4**). This implies that the resonance effects by the methoxy group might play an important role for the reaction.

Table 1. Homologation of SmI_2 mediated reaction

Substrate[a]		Product	Isolated Yield[b],%
	1a 1b	 7	72 60
	2a 2b	 8	45 40
	3a 3b	 9	39 0
	4a 4b	 10	21 0
	5a 5b	 11	84 68
	6a 6b	 12	64 64

[a]Compound **a**: X = I, Compound **b**: X = Br. [b]Structures of all products were identified by ^{1}H NMR, IR, GC-MS.



Scheme 1

The reaction of **1** or **2** appears to proceed *via* formation of an intermediate **A** by attacking of samariumalkyl chain on the carbonyl group of the amide (Scheme 1). Strong oxophilicity between Sm (III) ion and oxygens may make the formation of **A**. The amino group in the intermediate with a methoxy group at the *ortho* position (**A**) might act as a relatively good leaving group *via* stabilization of amine anion by samarium (III) to give an aldehyde (**B**), which is further reduced by SmI_2 to a ketyl radical that abstracts hydrogen from the reaction medium[10] to give an one-carbon homologated alcohol. In the case of the *meta* or *para*-methoxy substituted substrates, formation of such a chelate intermediate is impossible. The oxygen in the intermediate with a methoxy group at the *meta* or *para* position (**C**) is a relatively good leaving group, giving cyclic iminium ion (**D**), which is converted by SmI_2 to cyclic products (Scheme 1).

Generally, the reaction of *N*-iodoalkylformamides (**1b-6b**) gave the expected products (**7-12**) in relatively lower yields compared to those of *N*-bromoalkylformamides (**1a-6a**) (Table 1). The reason is not clear. We could not find a separable major spot on TLC.

The details of mechanistic studies and the further studies for the other homologous series are under investigation.

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9. The general samarium diiodide reaction of the formamide is as follows. A solution of *N*-haloalkylformamide (0.1 M) in THF was slowly added to a solution of SmI_2 (3.5 equiv.) and HMPA (4 equiv.) in THF at −78 °C. The reaction mixture was stirred for 1 h and then gradually warmed to room temperature. The reaction was completed in 12 h. After the reaction was quenched by addition of ammonium hydroxide solution, the reaction mixture was concentrated and chromatographed on silica gel. In these reactions, 3.5 equiv. of SmI_2 and 4 equiv. of HMPA are necessary for completion of the reaction. Otherwise, unreacted starting material was observed. Reference of SmI_2 solution preparation: Molander, G. A. and McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.
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11. **Compound 7** ^{1}H NMR($CDCl_3$, 300 MHz): δ 6.62-6.90 (m, 4H), 3.84 (s, 3H), 3.70 (t, 2H, J = 6.00 Hz), 3.18 (t, 2H, J = 6.27 Hz), 1.67-1.78 (m, 4H). MS m/z : 195 (M^+). IR (KBr, cm^{-1}): 3416, 2938, 1602, 1514, 1456, 1250, 1222, 1028, 736. **Compound 8** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.60-6.88 (m, 4H), 3.85 (s, 3H), 3.68 (t, 2H, J = 6.21 Hz), 3.15 (t, 2H, J = 6.99 Hz), 1.44-1.75 (m, 6H). MS m/z: 209 (M^+). IR (KBr, cm^{-1}): 3418, 2934, 1602, 1514, 1456, 1248, 1222, 1030, 736. **Compound 9** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (t, 1H, J = 8.19 Hz), 6.26-6.20 (m, 2H), 6.14 (s, 1H), 3.82 (s, 3H), 3.29 (t, 4H, J = 6.45 Hz), 2.01 (t, 4H, J = 6.45 Hz). MS m/z: 177 (M^+). IR (KBr, cm^{-1}): 2960, 2833, 1608, 1500, 1383, 1222. **Compound 10** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.12 (t, 1H, J = 8.0 Hz), 6.07-6.20 (m, 2H), 6.08 (s, 1H), 3.79 (s, 3H), 2.91 (t, 4H, J = 5.42 Hz), 1.51-1.60 (m, 4H), 1.40 (t, 2H, J = 5.32 Hz). MS m/z: 191 (M^+). IR (KBr, cm^{-1}): 2962, 2828, 1618, 1514, 1488, 1370, 1238, 1178, 1044. **Compound 11** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.87 (d, 2H, J = 8.9 Hz), 6.55 (d, 2H, J = 8.9 Hz), 3.78 (s, 3H), 3.25 (t, 4H, J = 6.54 Hz), 2.00 (t, 4H, J = 6.54 Hz). MS m/z: 177 (M^+). IR (KBr, cm^{-1}): 2962, 2828, 1618, 1514, 1488, 1370, 1238, 1178, 1044, 814. **Compound 12** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.82 (d, 2H, J = 9.15 Hz), 6.72 (d, 2H, J = 9.15 Hz), 3.67 (s, 3H), 2.93 (t, 4H, J = 5.49 Hz), 1.57-1.65 (m, 4H), 1.45 (quint, 2H, J = 5.49 Hz). MS m/z: 191 (M^+). IR (KBr, cm^{-1}): 2962, 2828, 1618, 1514, 1488, 1370, 1238, 1178.