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Comparative study of TmI_2, SmI_2, and SmI_2/HMPA in the cross-coupling reactions of 2-acetylthiophene and thiophene-2-carboxylate with carbonyl compounds

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Abstract—The cross-coupling reactions of acetylthiophene or ethyl thiophene-2-carboxylate with aldehydes or ketones were achieved in a regioselective manner by using thulium diiodide in THF solution. Similar coupling reactions were also realized by using samarium diiodide together with excess amounts of hexamethylphosphoramide (HMPA). However, ethyl thiophene-2-carboxylate was inert in SmI_2/THF solution, and acetylthiophene was simply reduced to thienylethanol by SmI_2 in the absence of HMPA.

Samarium diiodide (SmI_2) has become a popular one-electron-transfer reducing agent in organic synthesis.[1,2] Hexamethylphosphoramide (HMPA) is a reagent generally used to enhance the reduction potential of SmI_2 in THF solution.[3] Although this protocol is successful in a variety of organic reactions, one should take caution in using HMPA due to its suspected cancer inducing property.[4] It is thus desirable to have an HMPA-free reagent that can behave similarly as SmI_2/HMPA in organic synthesis. Along this line, thulium diiodide (TmI_2)[5] and dysprosium diiodide (DyI_2)[6] having higher reduction potential than SmI_2 are considered good candidates.[7] Evans et al. have shown that TmI_2 exhibits a reactivity equivalent or even superior to SmI_2/HMPA in the coupling reactions of ketones with alkyl halides.[5] For example, treatment of cyclohexanone and 2-phenylethyl iodide by TmI_2 or SmI_2/HMPA at room temperature in THF solutions affords the coupling product, 1-(2-phenylethyl)-1-cyclohexanol, in high yields (>80%). Without the assistance of HMPA, SmI_2 can only reduces phenylethyl iodide in the refluxing THF solution.[1b]

Due to its oxophilic nature, SmI_2 is also extensively utilized to effect the coupling reactions of carbonyl compounds.[1,2] The extraordinary effect of HMPA has been observed. For example, benzaldehyde generally undergoes a pinacol coupling reaction on treatment with SmI_2 in THF solution.[1] However, Fang and co-workers have found a phenyl–carbonyl coupling product, 4-(1-hydroxybenzyl)benzaldehyde, when benzaldehyde is treated with SmI_2 in the presence of HMPA.[8] In the latter reaction, coordination of several HMPA molecules on samarium ion exerts a severe steric hindrance around the ketyl center to prevent the pinacol coupling between two ketyl sites. Instead, the benzaldehyde ketyl undergoes electron delocalization, and reacts at the remote *para*-position to furnish the phenyl–carbonyl coupling product. The crucial role of HMPA is also found in various self- and cross-aryl–carbonyl coupling reactions of acetophenones,[8] indolecarbaldehydes,[9] thiophenecarbaldehydes,[10] and thiophenecarboxylates.[11]

In order to make a comparison of TmI_2 with SmI_2 in the presence or absence of HMPA, we investigated the function of TmI_2 in the cross-coupling reactions of 2-acetylthiophene (**1**) and ethyl thiophene-2-carboxylate (**2**) with carbonyl compounds. The similarity and difference in the chemo-, regio-, and stereoselectivities are demonstrated in these reactions using SmI_2, SmI_2/HMPA, or TmI_2.

Depending on the reaction conditions, there are several possible reaction pathways when acetylthiophene was

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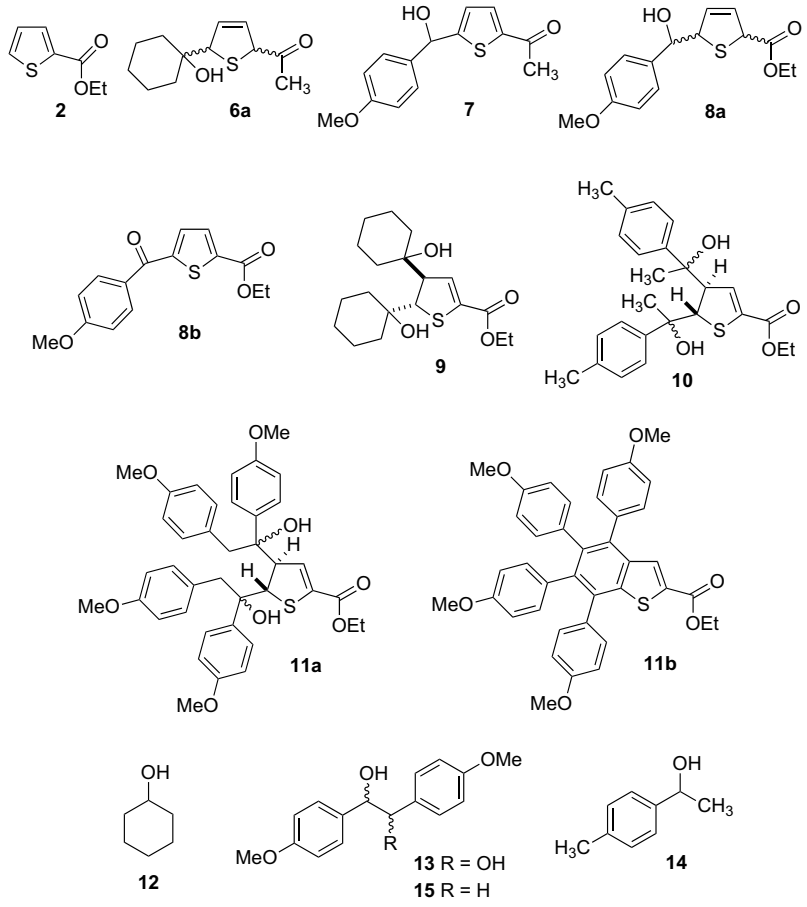
treated with SmI_2 or TmI_2 (Scheme 1). The first one-electron transfer from MI_2 (M represents Tm or Sm) could generate the ketyl intermediate **A**. Abstraction of a hydrogen atom from THF solvent could give a reduction product, 1-(thien-2-yl)ethanol (**3**) (reaction type i). Indeed, the reduction product was obtained when 2-acetylthiophene was treated with SmI_2 in the absence of HMPA (Table 1, entries 1 and 4). No cross-coupling product **4** (reaction type ii) was observed in any case. The ketyl intermediate **A** might be further reduced by a second equivalent of MI_2 to give the organometallic intermediates **B** and **C**.[12] The intermediate **B** might be stabilized by chelation, whereas the adjacent sulfur atom with empty d-orbitals might stabilize the intermediate **C**. The cross-coupling reaction of **B** with another carbonyl compound would give a C-3 coupling product **5** (reaction type iii), whereas the reaction of **C** would afford a C-5 coupling product **6** (reaction type iv). Our study revealed the effective formation of C-5 coupling products under appropriate reaction conditions, while no C-3 coupling product was observed.

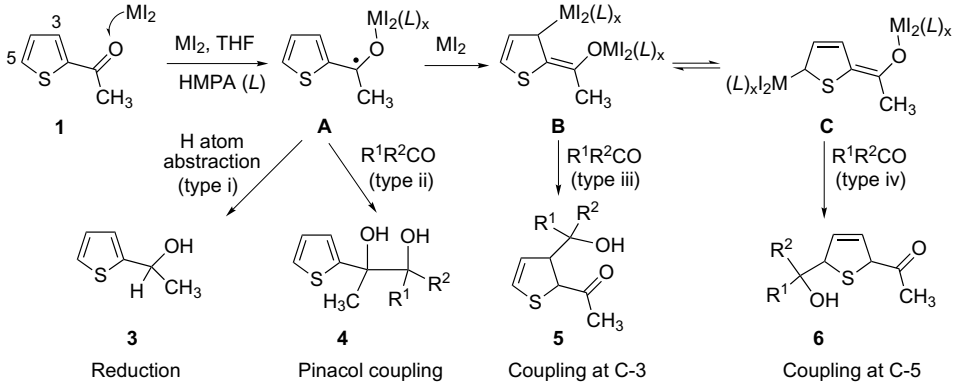
(method B),[11b] and using TmI_2 in the absence of HMPA (method C). The following procedure for the TmI_2 promoted coupling reactions is typical.

Method C: Under an atmosphere of argon, a greenish solution of TmI_2 was prepared by dissolving $TmI_2(THF)_{2.8}$ (756 mg, 1.2 mmol) in THF (10 mL) at room temperature (25 °C). To the cooled TmI_2 solution (in an ice bath) was added a THF solution (3 mL) of ethyl thiophene-2-carboxylate (73 mg, 0.5 mmol) and cyclohexanone (109 mg, 1.1 mmol). The reaction mixture was stirred at 0 °C for 20 min, and then at room temperature for 5 h. The resulting yellow mixture was then quenched by adding saturated aqueous NH_4Cl solution (1 mL). The reaction mixture was filtered through a short silica gel column, and rinsed with EtOAc/hexane (1:1). The filtrate was concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane 2:8 to give the desired three-component coupling product **9** (144 mg, 82%).[13]



The results for the SmI_2 and TmI_2 promoted reactions of 2-acetylthiophene and ethyl thiophene-2-carboxylate with carbonyl compounds are compiled in Table 1. In order to make a precise comparison, each set of reactions was conducted under three different conditions: using SmI_2 in the absence of HMPA (method A), using SmI_2 in the presence of excess amounts of HMPA

In the absence of HMPA (entries 1, 10, 13, and 16), SmI_2 generally reduced ketones to the corresponding alcohols, such as thienylethanol **3**, cyclohexanol **12**, 1-(*p*-tolyl)ethanol **14**, and 1,2-bis(4-methoxyphenyl)ethanol **15**. The reductive coupling reaction of 4-methoxybenzaldehyde also occurred under such reaction conditions to give pinacol **13** (entries 4 and 7). Without HMPA,



Scheme 1. The possible reactions of 2-acetylthiophene by the promotion of SmI_2 or TmI_2: (i) reduction to alcohol **3**, (ii) coupling with a carbonyl to pinacol **4**, (iii) coupling at C-3 with a carbonyl to hydroxyketone **5**, and (iv) coupling at C-5 with a carbonyl to hydroxyketone **6**.

Table 1. Comparison of TmI_2 and SmI_2 in the cross-coupling reactions of 2-acetylthiophene (**1**) and ethyl thiophene-2-carboxylate (**2**) with carbonyl compounds

Entry	Reactants (equiv)	Method[a]	Reaction time (h)	Coupling products (yields, %; ratio of isomers)	Other products (yields, %)	Recovered substrate (yields, %)
1	**1** (1)+Cyclohexanone (1)	A	10		**3** (87); **12** (77)	
2	**1** (1)+Cyclohexanone (1)	B	10	**6a** (41; 55:45)	**3** (35); **12** (20)	
3	**1** (1)+Cyclohexanone (1)	C	10	**6a** (41; 55:45)	**3** (23); **12** (29)	
4	**1** (1)+4-$MeOC_6H_4CHO$ (1)	A	2		**3** (24); **13** (81)	
5	**1** (1)+4-$MeOC_6H_4CHO$ (1)	B[b]	2	**7** (61)		
6	**1** (1)+4-$MeOC_6H_4CHO$ (1)	C[b]	2	**7** (60)[c]	**13** (21)	**1** (45)
7	**2** (1)+4-$MeOC_6H_4CHO$ (1)	A	2		**13** (85)	**2** (88)
8	**2** (1)+4-$MeOC_6H_4CHO$ (1)	B	2	**8a** (75; 19:30:15:36)[d]		
9	**2** (1)+4-$MeOC_6H_4CHO$ (1)	C	2	**8a** (74; 20:32:15:33)[d]		
10	**2** (1)+Cyclohexanone (2)	A	10		**12** (69)	**2** (87)
11	**2** (1)+Cyclohexanone (2)	B	10	**9** (89)		
12	**2** (1)+Cyclohexanone (2)	C	5	**9** (82)		
13	**2** (1)+4-MeC_6H_4COMe (2)	A	10		**14** (71)	**2** (80)
14	**2** (1)+4-MeC_6H_4COMe (2)	B	10	**10** (63; 61:39)		
15	**2** (1)+4-MeC_6H_4COMe (2)	C	10	**10** (53; 58:42)		
16	**2** (1)+$ArCOCH_2Ar$ (2)[e]	A	24		**15** (89)	**2** (84)
17	**2** (1)+$ArCOCH_2Ar$ (2)[e]	B	24	**11a** (48; 57:43)		
18	**2** (1)+$ArCOCH_2Ar$ (2)[e]	C	24	**11a** (31; 55:45)		

[a] Method A: SmI_2 (2.4 equiv) in THF. Method B: SmI_2 (2.4 equiv) and HMPA (16 equiv) in THF. Method C: TmI_2 (2.4 equiv) in THF. All the reactions were conducted by dropwise addition of a mixture of 2-acetylthiophene (0.5–1.0 mmol) (or ethyl thiophene-2-carboxylate) and carbonyl compound (0.6–2.2 mmol as indicated) in THF (1–3 mL) to the freshly prepared lanthanide diiodide solution in THF (10–20 mL) at 0 °C. The reaction mixture was stirred at 0–25 °C for the indicated period, and then quenched by addition of aqueous NH_4Cl solution.

[b] The product was obtained by exposure of the reaction mixture to air for 2 h before workup.

[c] The yield of **7** was calculated based on the consumed acetylthiophene.

[d] The mixture of four isomers was oxidized by PDC to give a single product **8b**.

[e] Ar represents 4-methoxyphenyl.

SmI_2 could not reduce thiophenecarboxylate; more than 80% of ester **2** was recovered under such conditions (method A, entries 7, 10, 13, and 16).

By the assistance of HMPA, SmI_2 promoted a cross-coupling reaction (Scheme 1, type iv) between 2-acetylthiophene and cyclohexanone to give product **6a** in 41% yield (entry 2). Compound **6a** consisted of two isomers (55:45), which were partially separated and characterized by their ^1H NMR spectra.[13] The combined reagent SmI_2/HMPA also effected the cross-thienyl–carbonyl coupling reaction between acetylthiophene and *p*-methoxybenzaldehyde (entry 5); after which the reaction mixture was stirred in air to furnish an oxidative aromatization product **7** in 61% yield.[13] Using the HMPA-free TmI_2 reagent induced the thienyl–carbonyl coupling reactions in a similar fashion to afford products **6a** and **7** in comparable yields (entries 3 and 6), as from the SmI_2/HMPA promoted reactions. Some reduction products (**3** and **12**) of 2-acetylthiophene and cyclohexanone as well as the pinacol **13** derived from *p*-methoxybenzaldehyde were also observed in the reactions using TmI_2 or SmI_2/HMPA.

Although ester **2** was inert to SmI_2 in THF solution, using TmI_2 or SmI_2/HMPA successfully effected the coupling reactions of ester **2** with various carbonyl compounds. The coupling reaction with *p*-methoxy-

benzaldehyde (1 equiv) occurred at the C-5 position of ester **2**, and the subsequent protonation at the C-2 position of the dienolate intermediate (analogous to intermediate **C**) furnished the 2,5-dihydrothiophene product **8a** (entries 8 and 9). Compound **8a** existed as a mixture of four isomers, which was oxidized by pyridinium dichromate to give a single product **8b**.[11a] On the other hand, the double electrophilic reaction of ester **2** with 2 equiv of cyclohexanone was realized by using SmI_2/HMPA or TmI_2 to give diol **9** in high yields (entries 11 and 12). Attack of the dienolate intermediate by the second cyclohexanone molecule should occur at the less hindered face to produce diol **9** with the 4,5-*trans* configuration, which was established by NMR analysis and X-ray diffraction method.[11b] Similarly, the three-component coupling reaction of ester **2** with 2 equiv of *p*-methylacetophenone was carried out by using SmI_2/HMPA or TmI_2, giving the diol product **10** as a mixture of two isomers[13] (entries 14 and 15). Because lanthanide ion is more oxophilic but less basic than alkali and alkaline metal ions,[14] the three-component coupling reaction of ester **2** with 1,2-bis(4-methoxyphenyl)ethanone, a highly enolizable ketone, was also realized by using SmI_2/HMPA or TmI_2 to afford the diol product **11a** (entries 17 and 18). The acid-catalyzed dehydration of **11a** (as a mixture of two isomers), followed by treatment with DDQ, furnished the oxidative cyclization product **11b**.[11b]

Through this study we found that TmI_2 and SmI_2 exhibited distinct reaction modes with 2-acetylthiophene. Using TmI_2 favored the thienyl–carbonyl coupling reaction, whereas using SmI_2 caused the reduction of the acetyl group. Thiophene-2-carboxylate was reactive with TmI_2, but inert to SmI_2 because it has a lower reduction potential than TmI_2.[7] By ligation with HMPA molecules, the reduction potential of SmI_2/HMPA was enhanced[14] to exhibit reactivity toward thiophene-2-carboxylate. Our study not only revealed the difference of TmI_2 from SmI_2, but also clearly indicated the similarity between TmI_2 and SmI_2/HMPA in promotion of the cross-coupling reactions of 2-acetylthiophene and thiophene-2-carboxylate with other carbonyl compounds. As shown in Table 1, TmI_2 and SmI_2/HMPA behave similarly in terms of chemo-, regio-, and stereoselectivities in the reaction protocols. Our finding showing the similarity of TmI_2 to SmI_2/HMPA but discrepancy from SmI_2 is remarkable. The detailed mechanism for these results is not fully understood, however, the effective size and inherent electronic nature of thulium and samarium ions may be important factors to account for the reaction modes.[3,15]

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13. The products were characterized by their physical and spectroscopic properties (mp, IR, MS, HRMS, ^1H, and ^{13}C NMR). Some pertinent data are listed. **6a**-major isomer: δ_H 5.97 (1H, dd, $J = 5.8$, 2.6 Hz, H-3), 5.66 (1H, dd, $J = 5.8$, 2.8 Hz, H-4), 4.52 (1H, d, $J = 2.8$ Hz, H-2), 4.29 (1H, d, $J = 2.6$ Hz, H-5), 2.53 (1H, br s, OH), 2.32 (3H, s), 1.69–1.46 (10H, m). **6a**-minor isomer: δ_H 6.22 (1H, dd, $J = 5.8$, 2.5 Hz), 5.75 (1H, dd, $J = 5.8$, 2.9 Hz), 4.89 (1H, d, $J = 2.9$ Hz), 4.80 (1H, d, $J = 2.5$ Hz), 2.97 (1 H, br s, OH), 2.86 (3H, s), 2.17–1.46 (10H, m). **7**: δ_H 7.16 (2H, d, $J = 9.0$ Hz), 7.09 (1H, dd, $J = 6.8$, 1.9 Hz), 6.87 (2H, d, $J = 9.0$ Hz), 6.76 (1H, dd, $J = 6.8$, 1.9 Hz), 5.86 (1H, s), 3.77 (3H, s), 2.27 (3H, s). **10**-major isomer: δ_H 7.21 (2H, d, $J = 8.2$ Hz), 7.09 (2H, d, $J = 8.2$ Hz), 7.06 (2H, d, $J = 8.2$ Hz), 6.97 (2H, d, $J = 8.2$ Hz), 6.20 (1H, d, $J = 3.4$ Hz), 4.20 (2H, q, $J = 6.8$ Hz), 3.98 (1H, dd, $J = 5.6$, 3.9 Hz), 3.60 (1H, dd, $J = 3.9$, 3.7 Hz), 2.33 (3H, s), 2.31 (3H, s), 2.00 (1H, br s, OH), 1.64 (1H, br s, OH), 1.46 (3H, s), 1.29 (3H, t, $J = 6.8$ Hz), 1.29 (3H, s). **10**-minor isomer: δ_H 7.26–7.04 (8H, m), 6.32 (1H, d, $J = 3.4$ Hz), 4.31 (2H, q, $J = 6.8$ Hz), 3.99 (1H, dd, $J = 4.2$, 3.0 Hz), 3.78 (1H, dd, $J = 4.2$, 3.5 Hz), 3.02 (2H, br s, OH), 2.31 (6H, s), 1.40 (3H, s), 1.33 (3H, t, $J = 6.8$ Hz), 1.32 (3H, s). Two isomers of

11a showed the diagnostic olefin proton (H-3, d, $J = 3.4$ Hz) at δ_H 6.27 and 6.24, respectively.

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