Samarium diiodide promoted coupling of thiophenecarbaldehydes

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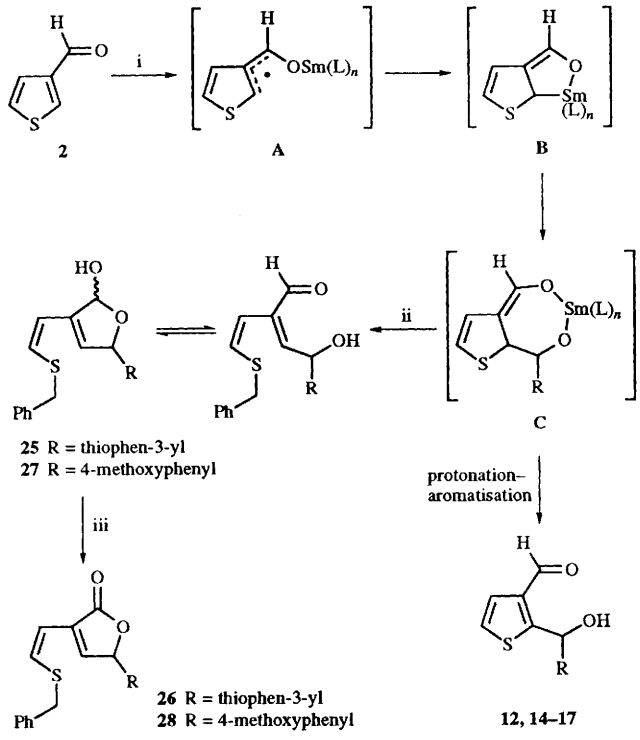
Thiophene-2-carbaldehyde adds to aromatic and aliphatic aldehydes with the mediation of samarium diiodide and hexamethylphosphoramide. These hydroxyalkylations occur at the 5-position of thiophene-2-carbaldehyde. The self- and cross-coupling reactions of thiophene-3-carbaldehyde occur at the 2-position. *S*-Alkylation of the reaction intermediates gives substituted γ-lactols.

Thiophenecarbaldehydes are generally reduced to the thiophenemethanols by catalytic hydrogenation[1] or by treatment with $LiAlH_4$[2] or Fe–HOAc.[3] On treatment with Mg–MgI_2 thiophenecarbaldehydes undergo self-coupling to give pinacols.[4] Electrochemical reductions of acetylthiophene or benzoylthiophene also give pinacols.[5] Reductions of alkanoylthiophenes with dissolved metals such as Li–NH_3 or Na–NH_3 give the 2,5-dihydro derivatives.[6] However, reductions of thiophenes to tetrahydrothiophenes are achieved with Et_3SiH–CF_3CO_2H.[7] We demonstrated previously that bimolecular reduction of benzaldehydes[8] or indolecarbaldehydes,[9] by way of aryl–carbonyl couplings, occur with SmI_2 in the presence of hexamethylphosphoramide (HMPA) whereas pinacol couplings are diminished under these conditions. We report herein the self- and cross-coupling of thiophenecarbaldehydes **1** and **2** promoted by SmI_2–HMPA. The thiophene–carbonyl coupling products were trapped with halogenalkanes and the products were elaborated to butenolides.

As shown in Table 1, acceptor substrates include benzaldehydes **3** and **6**, a pyrrolecarbaldehyde **4** and an aliphatic aldehyde **5**. The cross-coupling of thiophene-2-carbaldehyde and thiophene-3-carbaldehyde (entry 2) gave a product **8**, indicating the former aldehyde served as the donor whereas the latter aldehyde served as the acceptor. The reactions occurred *via* thiophene–carbonyl couplings although small amounts of products such as **13** and **19** derived from pinacol couplings were also found (entries 6 and 8). The pinacol of thiophene-3-carbaldehyde and 1-methylpyrrole-2-carbaldehyde might transfer a hydride to thiophene-3-carbaldehyde, so that both the reductive product, 3-thienylmethanol **18**, and the oxidative product, **19**, were obtained in nearly equal amounts.

Oxidation of alcohols **7**–**11** with pyridinium dichromate–molecular sieves (PDC–MS) gave the corresponding solid ketones **20**–**24**. The intermediate in the self-coupling of thiophene-3-carbaldehyde was trapped with benzyl bromide to give lactol **25** (65%, two epimers), which was transformed into lactone **26** (79%) on treatment with PDC–MS (Scheme 1). The intermediate in the cross-coupling of thiophene-3-carbaldehyde and 4-methoxybenzaldehyde also underwent *S*-alkylation. The reaction mechanism presumably involved sequential electron-transfer from SmI_2 (2 equiv.) to thiophene-3-carbaldehyde, giving an organosamarium intermediate **B**, which was stabilised synergetically by the adjacent sulfur atom and by co-ordination with the oxygen ion.

Thiophenecarbaldehydes are conventionally converted into the corresponding α-amino alkoxides[10] which react with electrophiles to give substituted thiophenecarbaldehydes. This one-pot reaction requires, however, sequential treatment with amine (such as *N*-methylpiperazine) and BuLi (several molar proportions) at low temperatures. The regiochemistry of the reaction varies depending on the reaction conditions. Our



Scheme 1 *Reagents and conditions:* i, **2** (2 mmol) or **2** (1 mmol)–RCHO (1.2 mmol), SmI_2 (3.65 mmol), THF (42 cm^3), HMPA (16 mmol), 0 °C, 10 min; ii, $PhCH_2Br$ (2 mmol), 0 to 27 °C, 25 h; iii, PDC, MS (4 Å), CH_2Cl_2, 27 °C, 3–8 h; yields: **25**, 65; **26**, 79; **27**, 63; **28**, 70

present method is relatively simple and gives products with predictable regiochemistry. The SmI_2-promoted thiophene–carbonyl coupling is likely to be applicable to acetylthiophenes† of which hydroxyalkylations cannot be realised by the conventional methods.

Experimental

General procedure

Under an atmosphere of argon, Sm (660 mg, 4.4 mmol) and 1,2-diiodoethane (1.03 g, 3.65 mmol) were stirred in anhydrous tetrahydrofuran (THF, 40 cm^3) until a dark blue solution formed. HMPA (2.8 cm^3, 16 mmol) was added and then the solution was cooled to 0 °C, after which a mixture of thiophene-2-carbaldehyde (the donor substrate, 0.094 cm^3, 1.0 mmol) and

† SmI_2–HMPA promoted dimerisation of acetophenone (phenyl–carbonyl coupling) was reported in ref. 8.

Table 1 Coupling of thiophenecarbaldehydes promoted by SmI_2 in THF and HMPA

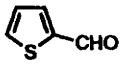
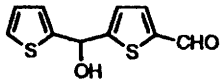
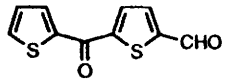
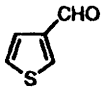
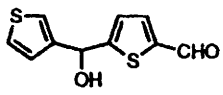
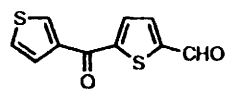
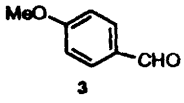
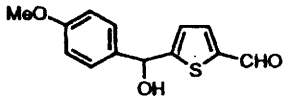
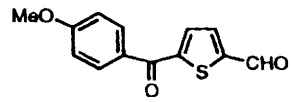
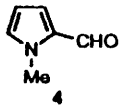
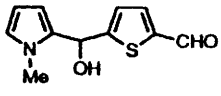
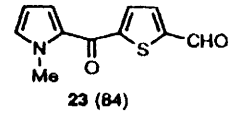
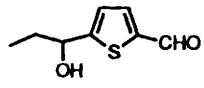
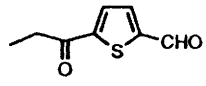
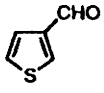
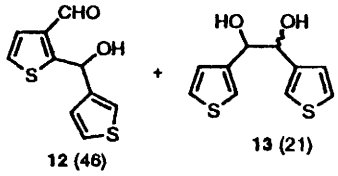
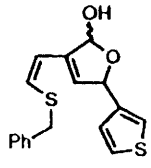
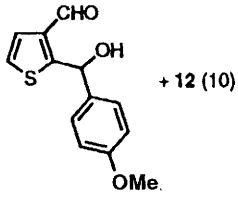
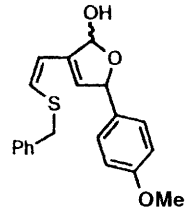
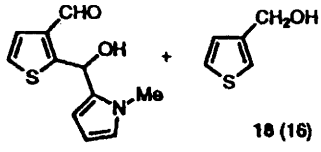
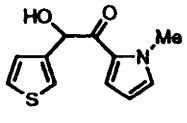
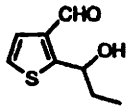
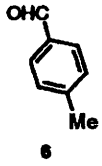
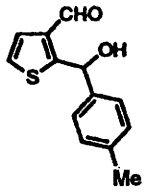
Entry	Donor	Acceptor	Coupling products (yield / %)	Reagents	Products (yeild / %)
1	 **1**	**1**	 **7 (49)**	PDC–MS	 **20 (89)**
2	**1**	 **2**	 **8 (45)**	PDC–MS	 **21 (83)**
3	**1**	 **3**	 9 (45)	PDC–MS	 **22 (86)**
4	**1**	 **4**	 **10 (36)**	PDC–MS	 **23 (84)**
5	**1**	 **5**	 + **7** (24) **11 (49)**	PDC–MS	 **24** (72)
6	 **2**	**2**	 **12** (46) + **13** (21)	$PhCH_2Br$	 **25** (65)
7	**2**	**3**	 + **12** (10) **14** (43)	$PhCH_2Br$	 **27** (63)
8	**2**	**4**	 **18** (16) **15** (21)		
			 + **12** (14) **19** (14)		

Table 1 (*contd*)

Entry	Donor	Acceptor	Coupling products (yield / %)	Reagents	Products (yeild / %)
9	2	5	 + **12 (22)** **16 (43)**		
10	2	 **6**	 **17 (37)**		

4-methoxybenzaldehyde (the acceptor substrate, 0.146 cm^3, 1.2 mmol) in THF (2 cm^3) were added dropwise. The mixture was stirred for 10 min at 0 °C and 30 min at room temperature (27 °C). The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the mixture was filtered through a pad of silica gel to remove HMPA. The residue was concentrated and chromatographed on a silica gel column by elution with EtOAc–hexane (2:8) to give the product **9** (102 mg, 45%). About 10–20% of the thiophene-2-carbaldehyde was recovered.

The coupling reactions of thiophene-3-carbaldehyde was carried out by similar procedures. In entries 6 and 7, the intermediates obtained by addition of the appropriate aldehyde at 0 °C for 10 min, were treated with benzyl bromide (0.224 cm^3, 2.0 mmol) for 24 h at room temperature (27 °C) to give lactols **25** (205 mg, 65%) and **27** (213 mg, 63%), respectively, after the usual work-up.

All new compounds had compatible IR, mass, high-resolution mass, ^1H and ^{13}C NMR spectra. Some pertinent data are listed: **8**, δ_H(200 MHz; $CDCl_3$; *J*/Hz) 9.80 (1 H, s), 7.61 (1 H, d, *J* 3.8), 7.33–7.29 (2 H, m), 7.06 (1 H, dd, *J* 4.6, 1.6), 6.99 (1 H, d, *J* 3.8), 6.10 (1 H, s), 2.96 (1 H, br s, OH). **12**, δ_H(200 MHz; $CDCl_3$; *J*/Hz) 9.92 (1 H, s), 7.43 (1 H, d, *J* 5.1), 7.27 (2 H, m), 7.20 (1 H, d, *J* 5.1), 7.08 (1 H, dd, *J* 4.4, 1.9), 6.42 (1 H, d, *J* 4.9), 4.43 (1 H, d, *J* 4.9, OH). **14**, δ_C(50 MHz; $CDCl_3$) 186.0 (d), 159.6 (s), 159.5 (s), 136.1 (s), 133.9 (s), 129.8 (d), 127.9 (d, 2 C), 124.2 (d), 113.8 (d, 2 C), 70.2 (d), 55.2 (q). **15**, δ_H(200 MHz; $CDCl_3$; *J*/Hz) 9.86 (1 H, s), 7.46 (1 H, d, *J* 5.2), 7.22 (1 H, d, *J* 5.2), 6.60 (1 H, dd, *J* 2.7, 1.8), 6.37 (1 H, d, *J* 5.7), 5.99 (1 H, dd, *J* 3.6, 2.7), 5.86 (1 H, dd, *J* 3.6, 1.8), 4.15 (1 H, d, *J* 5.7, OH), 3.68 (3 H, s). **20**, mp 102–103 °C. **21**, mp 95.5–97 °C; δ_C(75 MHz; $CDCl_3$) 183.3 (d), 180.8 (s), 149.9 (s), 147.8 (s), 140.3 (s), 135.0 (d), 133.5 (d), 132.8 (d), 128.1 (d), 126.9 (d). **22**, mp 111–112 °C. **23**, mp 84–86 °C. **24**, mp 90.5–91.5 °C. **26**, δ_H(200 MHz; $CDCl_3$; *J*/Hz) 7.46 (1 H, d, *J* 1.9), 7.34–7.30 (7 H, m), 6.98 (1 H, dd, *J* 3.6, 1.6), 6.68 (1 H, d, *J* 10.7), 6.24 (1 H, d, *J* 10.7), 6.05 (1 H, d, *J* 1.9), 4.05 (2 H, s). **28**, δ_H(200 MHz; $CDCl_3$; *J*/Hz) 7.41 (1 H, d, *J* 1.9), 7.33–7.29 (5 H, m), 7.18 (2 H, dd, *J* 6.6, 2.0), 6.87 (2 H, dd, *J* 6.6, 2.0), 6.66 (1 H, d, *J* 10.5), 6.25 (1 H, d, *J* 10.5), 5.92 (1 H, d, *J* 1.9), 4.03 (2 H, s), 3.78 (3 H, s).

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