Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters

Tetrahedron Letters 48 (2007) 8687–8690

A one-pot silyl-Reformatsky olefination

James M. Smith and Michael F. Greaney*

University of Edinburgh, School of Chemistry, Joseph Black Building, King's Buildings, West Mains Road, Edinburgh EH9 3JJ, UK

Received 3 September 2007; revised 25 September 2007; accepted 4 October 2007
Available online 9 October 2007

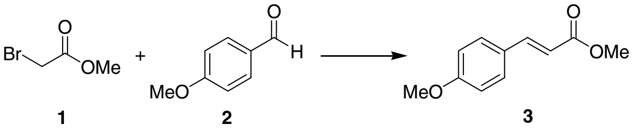
Abstract—A novel one-pot olefination reaction has been developed, involving the stereoselective formation of (*E*)-α,β-unsaturated esters/ketones from the reaction of α-bromocarbonyl compounds with aromatic aldehydes. The reactions use a reagent combination of trichlorosilane, and triethylamine and may proceed via the in situ formation of a trichlorosilyl ketene acetal. The general procedure offers key advantages (high conversions, low quantities of organic soluble by-products) over the conventional Wittig reaction.

Regioselective olefination methods such as the Wittig,[1] Julia–Lythgoe[2] and Peterson[3] reactions lie at the heart of organic chemistry and are indispensable for the construction of the carbon–carbon double bond. Since its discovery in 1953, the Wittig olefination in particular remains extremely popular in synthetic organic chemistry. The reaction features broad substrate scope, excellent functional group tolerance and high yields—frequently accompanied by good levels of discrimination between *E* and *Z* double bond geometric isomers in the olefin products. However, the drawbacks of the reaction in terms of atom economy[4] are well-documented—the generation of 1 equiv of triphenylphosphine oxide during the reaction, an organic soluble by-product, which usually requires separation from the olefin product, presents a major purification issue, especially when the reaction is carried out on an industrial scale. Many creative solutions have been developed to overcome this problem within the context of the Wittig reaction,[5] but alternative olefination reactions, which benefit from easier purification methods remain attractive research targets.

We now report a novel olefination reaction, using the common Wittig substrates of α-bromocarbonyl compounds and aromatic aldehydes, to give the corresponding (*E*)-α,β-unsaturated carbonyl products in moderate to good yields in a one-pot transformation. Our work began by studying the reaction of methyl α-bromoacetate **1** with anisaldehyde **2**, using a reagent combination of trichlorosilane and triethylamine. The corresponding olefin, **3**, was produced in a 39% yield (Table 1, entry 1). A screen of solvents and other variables revealed that the reaction performed better at lower temperatures (−10 °C) and using CH_2Cl_2 as a solvent, raising the yield to 59% (Table 1, entry 2).

Further optimisation centred on the use of Lewis basic additives in the reaction, several of which increased

Table 1. Olefination of anisaldehyde with methyl bromoacetate



Entry	Reagents	Solvent/temperature	Additive	Yield (%)
1	Cl_3SiH (1.5 equiv) NEt_3 (5 equiv)	MeCN/rt	—	39
2	Cl_3SiH (2 equiv) NEt_3 (5 equiv)	CH_2Cl_2/−10 °C to rt	—	59
3	Cl_3SiH (2 equiv) NEt_3 (5 equiv)	CH_2Cl_2/−10 °C to rt	Ph_3PO (0.1 equiv)	69

---

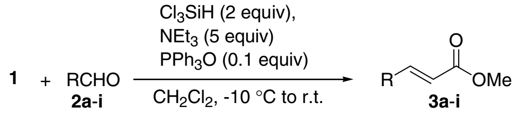
* Corresponding author. Tel.: +44 131 6504726; fax: +44 131 6504743; e-mail: Michael.Greaney@ed.ac.uk

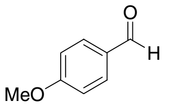
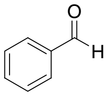
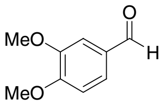
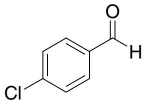
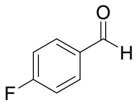
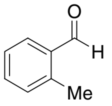
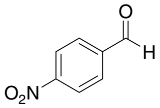
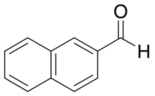
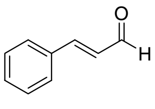
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.10.029

the yield, the best being a catalytic quantity of triphenylphosphine oxide. Under these conditions, product **3** could be isolated in a 69% yield (Table 1, entry 3).

The scope of the reaction was explored using a variety of aromatic aldehydes (Table 2). Yields were found to be higher in general for benzaldehydes bearing electron-releasing substituents on the aromatic ring (Table 2, entries 1, 3 and 6). An *ortho*-methyl group was well tolerated on the aromatic ring of the aldehyde (Table 2, entry 6), in contrast to the aromatic nitro functionality, which showed incompatibility towards the reaction conditions (Table 2, entry 7)—a very low yield of the desired product was observed. 2-Naphthaldehyde reacted as desired to give the corresponding olefin in a reasonable yield (Table 2, entry 8), and cinnamaldehyde was also a suitable substrate, allowing access to the α,β,γ,δ-unsaturated ester **3i**, although in this case the yield was low (Table 2, entry 9).

Table 2. Olefination of substituted benzaldehydes



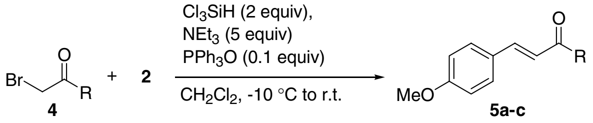
Entry	Aldehyde	Product yield[a] (%)
1		69
2		54
3		59
4		52
5		50
6		55
7		12
8		58
9		36

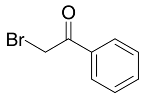
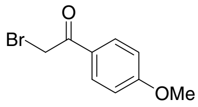
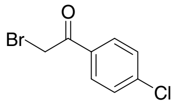
[a] Isolated yields after column chromatography.

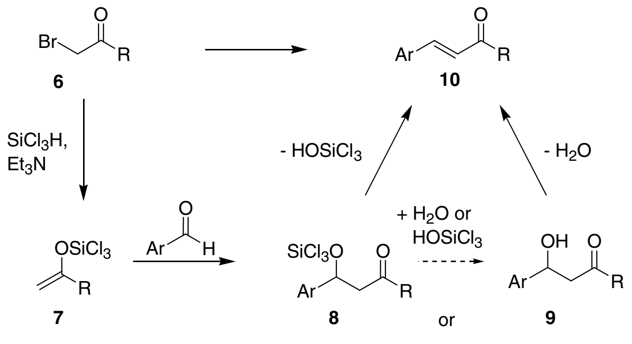
In all cases, the olefin was produced exclusively as the *E* isomer, with none of the *Z* isomer detected in any case, as established by ^{1}H NMR analysis of the crude reaction mixtures. The reaction could also be demonstrated efficiently in the case of α-bromoketones **4**—yields in these cases based on a short series were consistently high (Table 3). Attempts to extend this methodology further to aliphatic aldehydes and to ketones have been largely unsuccessful at this point in time, with only very small quantities of the desired olefin products detected in representative cases.

A reasonable mechanistic pathway for the general reaction is presented in Scheme 1. The α-bromocarbonyl compound **6** can react with the trichlorosilane in the presence of triethylamine, leading to the in situ formation of a silyl ketene acetal/silyl enol ether **7** in a 'silyl-Reformatsky'-type process.[6] The synthesis of trichlorosilylenol species through the direct reaction of trichlorosilane with α-halo-carbonyls is known for both α-bromoesters[7] and α-bromoketones.[8,9] Compound **7** may then react with the aldehyde to give (either) β-(trichlorosilyloxy)-carbonyl **8** or β-hydroxy-carbonyl **9** (the

Table 3. Olefination of bromoketones



Entry	Bromoketone	Product yield (%)
1		73
2		71
3		70



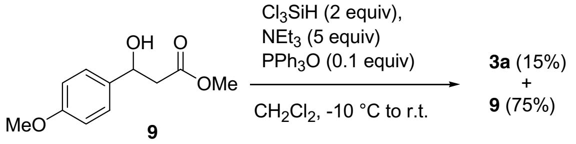
Scheme 1. Proposed reaction pathway.

former may be converted to the latter under the reaction conditions).[10] Elimination of either Cl_3SiOH (in the case of **8**) or H_2O (in the case of **9**) leads to the observed olefin product **10**.

In certain reactions, the presence of the β-hydroxycarbonyl intermediates **9** was detected in the crude ^1H NMR spectrum following work-up (the intermediate made up less than 10% of the yield in such reactions, as calculated by ^1H NMR integrals). In order to further confirm the propensity for this latter dehydration step, β-hydroxy-ester **9** was treated under the reaction conditions, and indeed the olefin product was detected, albeit in low conversion (Scheme 2). It is possible that the β-hydroxy-ester is formed in the olefination reaction itself mainly as the trichlorosilyl ether **8**, and that elimination for this compound is faster than for **9**.

When using an alternative base system in the reaction (1.8 equiv of $^iPr_2NEt$), a mixture of β-hydroxy-ester **9** and olefin **3a** was recovered, lending further credence to this mechanism (Scheme 3). The effect of triphenylphosphine oxide additive remains unclear, though it is possible that it may be acting as a Lewis base to activate the silyl ketene acetal towards electrophilic attack by the aldehyde, in analogy to Denmark's aldol chemistry of chlorosilyl enolates.[10] Studies showed that there was little effect on product yields upon raising the loading of the phosphine oxide beyond the 10 mol % level.[11]

In practical terms, the reaction is very easy to carry out, and the work-up is straightforward (the silane by-products are polymeric and can be removed easily by simple filtration following aqueous quenching).[12] In the case of the bromoester reaction, the large majority of the organic-soluble residue was the desired product (as observed by ^1H NMR of the crude material). In the case of the bromoketone reaction, in addition to the desired product, some debrominated ketone was also detected—this material is presumably formed by protonation of the trichlorosilyl enol ether intermediate. The reaction goes with full conversion with respect to the aromatic aldehydes (given the yields, a minor percentage of the aldehyde material may be lost through reduction by the silane—the resultant alcohol would then undergo further reactions with the silane to become integrated into the polymeric material).



Scheme 2. Dehydration of aldol product.

$$\mathbf{1} + \mathbf{2} \xrightarrow[\substack{Ph_3PO\ (0.1\ \text{equiv})\\ CH_2Cl_2,\ -10\ ^\circ C}]{\substack{Cl_3SiH\ (1.8\ \text{equiv})\\ ^iPr_2EtN\ (6\ \text{equiv})}} \mathbf{9}\ (45\%) + \mathbf{3a}\ (18\%)$$

Scheme 3. Formation of β-hydroxy-ester **9** using $^iPr_2NEt$.

In summary, a novel one-pot olefination reaction has been developed, producing *E*-olefins from α-bromocarbonyl compounds and aldehydes with high stereoselectivity, using the reagent combination of Cl_3SiH/NEt_3. Many aromatic aldehydes were found to be compatible with the reaction, which may proceed via the in situ generation of a trichlorosilyl enol ether or ketene acetal. Product yields were found to increase by the use of sub-stoichiometric quantities of Ph_3PO. Practically, this reaction represents a useful alternative to the standard Wittig procedure. Further exploration of the scope of the reaction with a wider variety of substrate classes and additives will be the focus of future work in this area.

Acknowledgement

We acknowledge the EPSRC for financial support.

References and notes

1. (a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44–57; (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927; (c) Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049–3066.
2. (a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836; (b) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763–768; (c) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829; (d) Blakemore, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.
3. (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784; (b) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195–200.
4. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
5. For examples of the use of solid-supported phosphines, perfluorinated phosphines and water-soluble phosphines in the Wittig reaction, see: (a) Westman, J. *Org. Lett.* **2001**, *3*, 3745–3747; (b) Galante, A.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2001**, *42*, 5425–5427; (c) Russell, M. G.; Warren, S. *Tetrahedron Lett.* **1998**, *39*, 7995–7998.
6. (a) Latouche, R.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* **1991**, *32*, 1179–1182; (b) Latouche, R.; Texier-Boullet, F.; Hamelin, J. *Bull. Soc. Chim. Fr.* **1993**, *130*, 535–546.
7. Inoue, Y.; Arai, M.; Miyoshi, T. Japanese Patent JP 03209387 A 19910912 1991; *Chem. Abstr.* **1991**, *116*, 83923.
8. Benkeser, R. A.; Smith, W. E. *J. Am. Chem. Soc.* **1968**, *90*, 5307–5309.
9. (a) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron* **1998**, *54*, 10389–10402; (b) Denmark, S. E.; Stavenger, R. A.; Winter, S. B. D.; Wong, K.-T.; Barsanti, P. A. *J. Org. Chem.* **1998**, *63*, 9517–9523.
10. (a) Denmark, S. E.; Winter, S. B. D. *Synlett* **1997**, *9*, 1087–1089; (b) Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333–2334; (c) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432–440; (d) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235; (e) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235–5248.
11. The possibility of the Ph_3PO additive ameliorating the yield via a minor Wittig reaction pathway was considered,

as Cl_3SiH/NEt_3 might be expected to reduce Ph_3PO to Ph_3P under the reaction conditions. Control experiments indicate that Ph_3PO does indeed undergo slow reduction to the phosphine under the reaction conditions. However, when the olefination of anisaldehyde was carried out using 10 mol % of Ph_3P, a lower isolated yield of 48% of **3a** was obtained (compared to 59% obtained in the absence of additives, Table 1, entry 2). This result suggests that either the Wittig pathway is not contributing at all, or that Ph_3P inhibits the silyl-Reformatsky pathway to a greater extent than the promotion of the Wittig pathway, to give an overall lower yield. On the basis of these and other experimental observations, it appears unlikely the Wittig pathway is operational.

12. *A typical reaction is carried out as follows*: To a stirred solution of triphenylphosphine oxide (56 mg, 0.2 mmol) and anisaldehyde (272 mg, 2 mmol) in anhydrous CH_2Cl_2 (6 mL) under N_2 at −10 °C was added methyl α-bromoacetate (704 mg, 4.6 mmol), followed by freshly distilled NEt_3 (1.01 g, 10 mmol), and finally Cl_3SiH (541 mg, 4 mmol), which was added in one portion. The resultant mixture was stirred at −10 °C for 8 h, then gradually warmed to rt overnight. The reaction was quenched by careful addition of satd aq $NaHCO_3$ (10 mL) followed by H_2O (20 mL). Et_2O (40 mL) was added, and the precipitate removed by filtration. The aqueous phase was further extracted with Et_2O (2 × 30 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/Et_2O, 3:1) providing methyl (*E*)-3-(4-methoxyphenyl)propenoate[13] **3a** (265 mg, 69%) as a white crystalline solid. ^1H NMR (250 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3); 3.84 (3H, s, Ar-OCH_3); 6.31 (1H, d, $J = 16.0$, $CHCO_2Me$); 6.91 (2H, d, $J = 8.9$, Ar-H); 7.48 (2H, d, $J = 8.9$, Ar-H); 7.66 (1H, d, $J = 16.0$, $CHCHCO_2Me$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 51.53, 55.34, 114.34, 115.28, 127.12, 129.74, 144.52, 161.43, 167.72.
13. Zhang, Z.; Wang, Z. *J. Org. Chem.* **2006**, *71*, 7485–7487.