ORGANIC
LETTERS

2005
Vol. 7, No. 12
2373−2376

Sulfoxides in Julia–Lythgoe Olefination: Efficient and Stereoselective Preparation of Di-, Tri-, and Tetrasubstituted Olefins

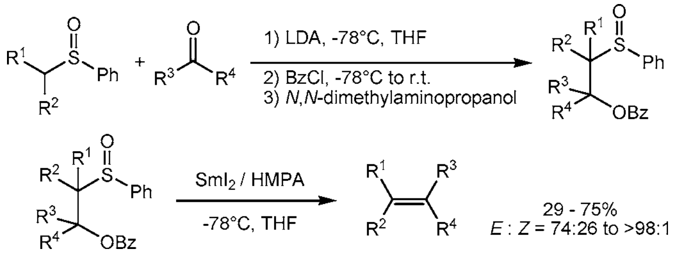
Jirí Pospíšil, Tomáš Pospíšil, and István E. Markó*

Université Catholique de Louvain, Département de Chimie, Bâtiment Lavoisier,
Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium

marko@chim.ucl.ac.be

Received March 26, 2005

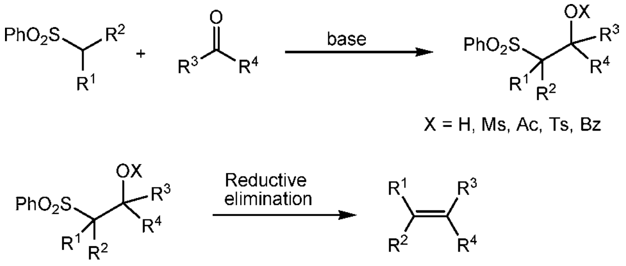
ABSTRACT



A novel modification of the classical Julia–Lythgoe olefination, using sulfoxides instead of sulfones, affords, after in situ benzoylation and SmI$_2$/HMPA- or DMPU-mediated reductive elimination, 1,2-di-, tri-, and tetrasubstituted olefins in moderate to excellent yields and *E*/*Z* selectivity. The conditions are mild, and the procedure is broadly applicable.

The formation of olefins from sulfones and carbonyl compounds, known as the Julia−Lythgoe olefination, is one of the most powerful tools of modern organic chemistry.[1] The initial reductive elimination of the intermediate β-hydroxysulfones using Na−Hg has been gradually superseded by mild, more selective, and less toxic reducing agents such as SmI$_2$[2] or Mg[3] (Scheme 1).

Scheme 1. Julia−Lythgoe Olefination



Disappointingly, this widely used method still suffers from several drawbacks. One of them is the relatively high stability of the sulfonyl anion which limits its reactivity. For example, if an additional electron-withdrawing substituent is present on the anion-bearing carbon, this organometallic species becomes so stable that it does not add even to activated

---

[1] (a) Dumeunier, R.; Markó, I. E. *Modern Carbonyl Olefination*; Takeda, T., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 104. (b) Kociensky, P. J. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 6. (c) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833. (d) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045. (e) Kocienski, P. J. *Phosphorus Sulphur* **1985**, *24*, 97.

[2] (a) Ihara, M.; Suzuki, S.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *Synlett* **1994**, 859. (b) Keck, G. E.; Savin, K. A.; Welgarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194. (c) Marko, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089. (d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (d) Inanaga, J. *Trends Org. Chem.* **1990**, *1*, 23.

[3] Lee, G. H.; Lee, H. K.; Choi, E. B.; Kim, B. T.; Pak, C. S. *Tetrahedron Lett.* **1995**, *36*, 5607.

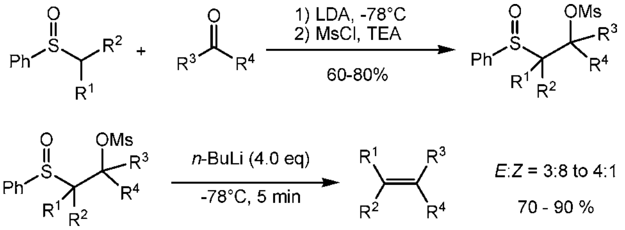
[4] I. Kuwajima, S.-J.; Sato, Y.; Kurata, A. *Tetrahedron Lett.* **1972**, *13*, 737.

[5] (a) Satoh, T.; Hanaki, N.; Yamada, N.; Asano, T. *Tetrahedron* **2000**, *56*, 6223. (b) Satoh, T.; Yamada, N.; Asano, T. *Tetrahedron Lett.* **1998**, *39*, 6935.

[6] The pK_a of the hydrogen on the carbon bearing sulfinyl group is four orders higher than the pK_a of the equivalent hydrogen on the carbon bearing sulfonyl group.

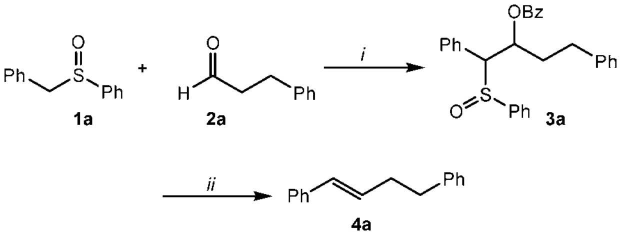
10.1021/ol050649e CCC: $30.25

Scheme 2. Sulfoxide Version of the Julia−Lythgoe Olefination



aldehydes.[2c] Moreover, in the case of the reaction of nonstabilized sulfones with some aldehydes and with ketones, the position of the equilibrium between the starting carbonyl compound and the sulfone anion is shifted toward the starting materials. The desired adduct (tertiary alkoxide) is therefore present in the reaction mixture as a minor component. Trapping this intermediate in situ with several electrophiles, such as benzoyl chloride, mesyl chloride, or acyl chloride, is a common trick employed to shift the equilibrium toward the products. It is interesting to note that these β-acyloxy, benzoyloxy, and mesyloxy sulfone derivatives undergo smoother reductive elimination than the parent β-hydroxy sulfones.

Table 1. Optimization of Reductive Elimination Step Using SmI_2



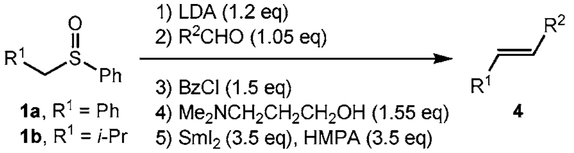
i) (a) LDA (1.1 eq), THF, -78°C; (b) BzCl (1.5 eq), -78°C to r.t. (c) $Me_2NCH_2CH_2CH_2OH$ (1.55 eq)
ii) SmI_2 (3.5 eq), THF, -78°C, additive

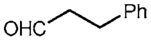
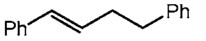
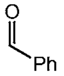
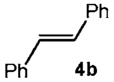
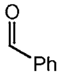
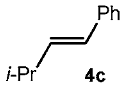
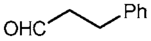
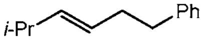
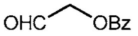
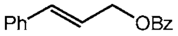
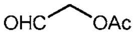
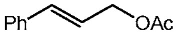
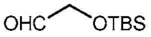
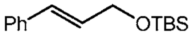
entry	additive	equiv to SmI_2	yield[a] (%)	*E*/*Z*[b]
1	–	–	–	na
2	HMPA	0.25	25	>95:1
3	HMPA	0.5	34	>95:1
4	HMPA	0.75	43	>95:1
5	HMPA	1.0	67	>95:1
6	HMPA	2.0	64	>95:1
7[c]	DMPU	15.0	12	na
8[d]	DMPU	15.0	32	>95:1
9[e]	DMPU	15.0	48	>95:1
10[f]	DMPU	15.0	10	na

[a] Overall yields refer to pure, isolated products. [b] Determined by capillary GC. [c] Reaction carried out at −50 °C. [d] Reaction carried out at −25 °C. [e] Reaction carried out at 0 °C. [f] Reaction carried out at rt.

Nevertheless, such modifications are useless when the generated sulfonyl anion is so stable that it does not add to the carbonyl compound. Recently, Satoh et al. reintroduced[4] sulfoxides as a sulfone equivalent in the Julia−Lythgoe olefination.[5] As an advantage, the carbanion generated α to the sulfoxide group is far less stabilized[6] than in the case of the corresponding sulfone and the addition reaction, leading to the formation of the C−C bond, is favored even in the case of ketones. The reductive elimination was carried out via sulfoxide/lithium exchange, followed by elimination of the β-mesyloxy or acyloxy group (Scheme 2).

Table 2. Synthesis of 1,2-Disubstituted Olefins



entry	1	R^2CHO	product	yield[a](%) *E* / *Z*[b]
1	**1a**		 **4a**	67%, >95:1
2	**1a**		 **4b**	75% >95:1
3	**1b**		 **4c**	70% 76:24
4	**1b**		 **4d**	69%, 94:6
5	**1a**		 **4e**	71%, >95:1
6	**1a**		 **4f**	68%, >95:1
7	**1a**		 **4g**	70%, >95:1

[a] Overall yields refer to pure, isolated products. [b] Determined by ^{1}H NMR spectroscopy.

Using this method, stilbene derivatives could be prepared via this Julia−Lythgoe modification for the first time, though with rather modest *E*/*Z* selectivity. On the other hand, the use of an excess (4 equiv) of a strong base (*n*-BuLi) can be rather inconvenient in the case of functionalized substrates.

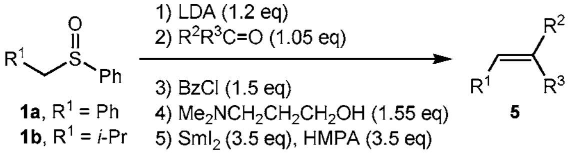
For some time, we have been interested in various modifications of the Julia−Lythgoe reaction[2c,7] and have recently introduced the SmI_2/HMPA-mediated reductive elimination of β-benzoyloxysulfones, formed by the addition of α-sulfone anions to ketones, as an efficient and stereoselective route toward trisubstituted olefins.

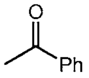
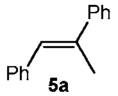
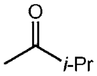
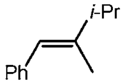
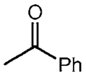
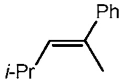
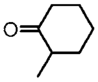
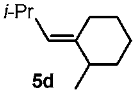
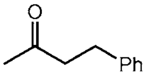
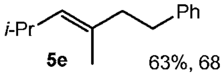
Based upon our previous results, we envisaged that the SmI_2-mediated reductive-elimination of β-benzoyloxy sul-

---

(7) Marko, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballaresb, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609.

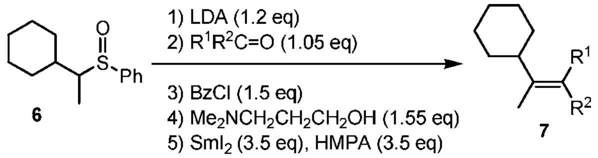
Table 3. Preparation of Trisubstitted Olefins

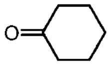
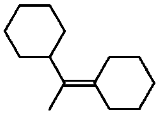
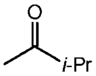
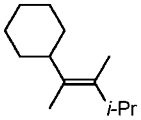
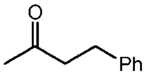
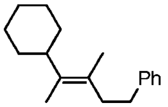


entry	1	$R^2R^3C{=}O$	product	yield[a](%) E / Z[b]
1	**1a**		 **5a**	51% 76:24
2	**1a**		 **5b**	57% 91:9
3	**1b**		 **5c**	64% 74:26
4	**1b**		 **5d**	64% 88:12
5	**1b**		 **5e**	63%, 68:32

[a] Overall yields refer to pure, isolated products. [b] Determined by ^{1}H NMR spectroscopy.

Table 4. Preparation of Tetrasubstituted Olefins



entry	$R^2R^3C{=}O$	product	yield[a](%) E / Z[b]
1		 **7a**	33%
2		 **7b**	29% 97:3
3		 **7c**	32% 91:9

[a] Overall yields refer to pure, isolated products. [b] Determined by ^{1}H NMR spectroscopy.

foxides might produce the desired olefins in high yield and with good *E*/*Z* selectivity.

To test our hypothesis, the coupling of sulfoxide **1a** with aldehyde **2a** was carried out (Table 1).[8] In the first step of this reaction, a new C−C bond is formed. As a consequence, two new stereogenic centers are created which, added to the one present in the sulfoxide moiety, leads to four different diastereoisomers of **3a**. To avoid their tedious separation, it was decided to use the mixture of adduct **3a** in the subsequent reductive elimination step.[9] Some pertinent results are collected in Table 1.

As can be seen in Table 1, SmI_2 itself does not promote the reaction (Table 1, entry 1). HMPA and DMPU were then tested as additives in order to increase the reduction power of SmI_2.[10] Gratifyingly, the presence of small amounts of HMPA already resulted in olefin formation, though the rate of the reaction was rather slow (Table 1, entry 2). The use of one equivalent of HMPA was found to be optimal, and adding more of this cosolvent did not increase the yield of the reaction (Table 1, entries 5 and 6).

DMPU was explored as an alternative, nontoxic HMPA equivalent. However, under all reaction conditions tested, the yields remained lower than with HMPA (Table 1, entries 7−10). Moreover, a large excess of DMPU and higher temperature (0 °C to rt) had to be employed (Table 1, entries 9 and 10).

Having devised suitable reaction conditions to effect this sulfoxide variant of the Julia−Lythgoe olefination, we explored its scope and limitations. A selection of pertinent results are collected in Tables 2 and 3.

The phenyl bearing sulfoxide **1a** gave, upon reaction with aryl and alkyl aldehydes, the corresponding disubstituted olefins **4a** and **4b** in good yields. Only the thermodynamically more stable (*E*)-double bond isomer was observed (Table 2, entries 1 and 2). The *iso*-propyl substituted sulfoxide **1b** afforded, upon reaction with dihydrocinnamaldehyde, the desired disubstituted olefin **4d** in good yield and a respectable 94:6 *E*/*Z* ratio (Table 2, entry 4). To our surprise, when **1b** was reacted with benzaldehyde, the resulting product **4c** was obtained with a modest *E*/*Z* ratio of 76:24 (Table 2, entry 3). When **1a** was reacted with methyl isopropyl ketone, the *E*-isomer **5b** was formed as the major product in a 91:9 ratio (Table 3, entry 2). Moreover, we were delighted to observe that even acetophenone did react under these conditions and afforded the desired olefin **5a** in 51% yield and with an *E*/*Z* ratio of 76:24. Essentially the same ratio of isomers was observed when **1b** was condensed with acetophenone. Olefin **5c** was formed in 64% yield and a 74:26 E/Z ratio (Table 3, entry 3). The reaction of **1b** with other

---

[8] All the reactions presented in Table 1 are carried out on the mixture of adduct **3a**.

[9] The excess of benzoyl chloride was reacted with *N*,*N*-dimethyl-3-aminopropanol and the amines was removed upon acidic workup.

[10] (a) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flowers, R. A., II. *Tetrahedron Lett.* **1998**, *39*, 4429. (b) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137. (c) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008. (d) Dahlen, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393.

[11] Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713.

dialkyl substituted ketones (Table 3, entries 4 and 5) gave olefins **5d** and **5e** in a respectable 88:12 and a reasonable 68:32 *E*/*Z* ratio, respectively.

Finally, to test the robustness of our method, the preparation of tetrasubstituted alkenes was attempted, using the sterically hindered sulfoxide **6**.[11] We were delighted to observe that the expected olefins **7** were formed in an excellent *E*/*Z* ratio and still acceptable yields (Table 4).

In summary, we have developed a novel, highly stereoselective method for the synthesis of 1,2-di-, tri-, and tetrasubstituted olefins.[12] Under our conditions, sterically hindered sulfoxide anion (such as the one derived from sulfoxide **6**) and unreactive ketones (e.g., acetophenone) could be coupled in good to acceptable yields. A variety of functions and protecting groups are also tolerated (Table 2, entries 5−7).

Further studies are now directed toward optimizing these conditions, broadening the scope of this method and applying it to relevant natural product synthesis.

Acknowledgment. Financial support by the Université Catholique de Louvain, Rhodia Ltd. (studentship to J.P) and Socrates-Erasmus program (studentship to T.P.) is gratefully acknowledged. I.E.M. is grateful to Rhodia for the 2001 Rhodia Outstanding Award.

Supporting Information Available: Experimental procedures, characterization of new compounds, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050649E

---

(12) **Typical Experimental Procedure. Coupling Step.** A solution of sulfoxide (1.0 mmol) in dry THF (10 mL, 0.1 M solution) was cooled to −78 °C and LDA (550 μL, 1.1 mmol) was added dropwise. The color of the mixture changed from slightly yellow to orange/red. After the mixture was stirred at −78 °C for 30 min, the aldehyde/ketone (1.05 mmol), dissolved in dry THF (0.5 mL), was added dropwise, and the mixture was stirred for an additional 2 h at −78 °C. Benzoyl chloride (1.5 mmol) in dry THF (0.5 mL) was then added, the resulting mixture was stirred for 30 min at −78 °C and then allowed to warm to rt over 1 h. After an additional 30 min at rt, $Me_2N(CH_2)_3OH$ (1.55 mmol) was added and the resulting suspension was stirred for 10 min at rt. The suspension was then diluted with Et_2O/H_2O = 1:1 (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with 1.0 M aq HCl (10 mL), H_2O (10 mL), and brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the crude product, which was used without additional purification in the subsequent step. **Reductive Elimination.** To a solution of SmI_2 (35 mL, 0.1 M in THF, 3.5 equiv) was added HMPA (613 μL, 3.5 equiv), and the mixture was cooled to −78 °C. The crude coupled product (1.0 mmol) in dry THF (0.5 mL) was added dropwise, and the resulting mixture was stirred at −78 °C for an additional 30 min. Then, aqueous satd NH_4Cl (20 mL) was added, and the whole was allowed to warm to rt. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The pooled organic layers were washed with 10% aq $Na_2S_2O_3$ (20 mL), H_2O (20 mL), and brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was then purified by chromatography on silicagel.