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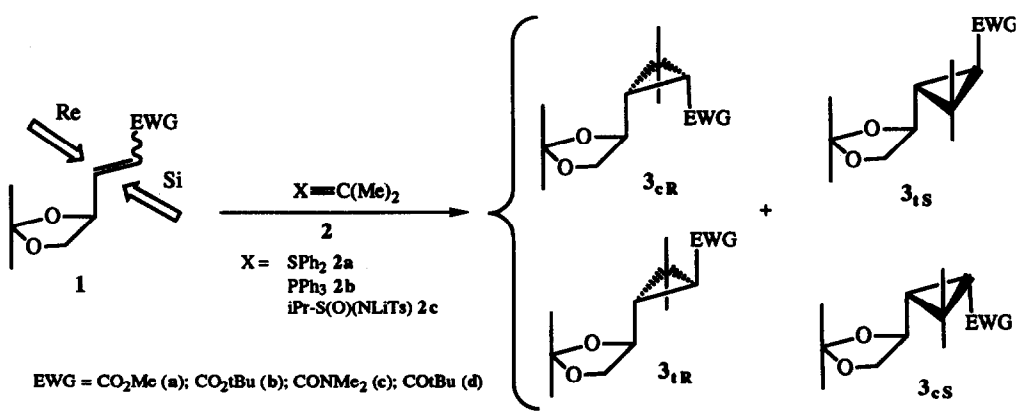
Stereoselective Syntheses of Cyclopropane Derivatives from γ-Alkoxy-α,β-Unsaturated Carbonyl Compounds and Isopropylidene Transfer Reagents

Alain Krief *, Phillipe Lecomte

Department of Chemistry, Facultés Universitaires Notre-Dame de la Paix, 61 rue de Bruxelles B-5000, Namur (Belgium).

Abstract: Asymmetric induction of isopropylidene diphenylsulfurane, -triphenylphosphorane and 2-lithio-2-propyl N-tosyl isopropyl sulfoximine towards Z- and E-γ-alkoxy-α,β-unsaturated t-butyl esters, N,N-dimethyl amides and t-butyl ketones derived from D-glyceraldehyde is disclosed.

In the course of a work directed towards the synthesis of chrysanthemic acids, we had the opportunity to react isopropylidene diphenylsulfurane [1] and -triphenylphosphorane [2] with γ-alkoxy-α,β-unsaturated esters derived from D-glyceraldehyde [3-12] **1a** and tartaric acid [4-12] **4** and found that they produce cyclopropane carboxylates [3-12] in reasonably good yield and with high stereospecificity in the case of the sulfur ylide [5-9,11,12] (cis- and trans-cyclopropanes from Z- and E-olefins respectively) and with complete stereoselectivity in the case of its phosphonium analogue (trans-cyclopropanes from Z- or E-olefins).[3,4,6-10] We also observed a surprising difference of reactivity between these two series of reagents since the former delivered the isopropylidene moiety by the Re-face both from the E- and Z-esters **1** whereas the later still reacted by the Re-face on the Z-**1** but attacked the Si-face of its E-stereoisomer. Our results where particularly surprising since both reagents were very closely related. [3-12]



Scheme 1

Several other reagents proved to react towards γ-alkoxy-α,β-unsaturated esters like isopropylidenediphenylsulfurane or like isopropylidenetriphenylphosphorane.[13-25] Surprisingly, some of them

belonging to the same class (involving for example a concerted, ionic or radical pathway) reacted differently whereas others which belong to very different classes react similarly. Unfortunately no unified rational has been, to our knowledge, reported. Furthermore most of the work reported so far has been mainly performed on esters.

We decided to undertake further work involving other γ-alkoxy-α,β-unsaturated carbonyl compounds and ylides able to transfer an isopropylidene moiety.

We now report that γ-alkoxy-α,β-unsaturated t-butyl esters, N,N-dimethyl amides as well as t-butyl ketones derived from D-glyceraldehyde behave, towards isopropylidene -diphenylsulfurane [1] and -triphenylphosphorane,[2] similarly to the methyl esters used in the previous work (scheme 1, table entries 1 to 8 columns **2a**, **2b**). Some minor differences nevertheless exist and will be discussed below. We also found that the reactivity and the selectivity of 2-lithio-2-propyl N-tosyl isopropyl sulfoximine [26] are closely related to those of isopropylidenetriphenylphosphorane (Scheme 1, table entries 1 to 8 column **2c**, compare to columns **2b** and **2c**).

Entry	1 EWG	1 Z/E	**2a** $Ph_2S{=}CMe_2$ *a,b **Yield in 3** [3_c(R/S)/3_t(R/S)]	**2b** $Ph_3P{=}CMe_2$ *c **Yield in 3** [3_c(R/S)/3_t(R/S)]	**2c** $Me_2CS(O)(NTs)CLiMe_2$ *d **Yield in 3** [3_c(R/S)/3_t(R/S)]
1	CO_2Me	Z	**84**[a], **71**[b] [100 (98/2)/0]	**61** [0/100 (94/6)]	**48** [0/100 (62/38)]
2	CO_2tBu	Z	**59**[b] [100 (99/1)/0]	**84** [4/96 (98/2)]	**91** [16(not studied)/84 (67/33)]
3	$CONMe_2$	Z	**61**[b] [100 (100/0)/0]	**60** [0/100 (91/9)]	**89** [0/100 (44/56)]
4	COtBu	Z	**80**[a] [100 (99/1)/0]	**57** [0/100 (90/10)]	**61** [0/100 (61/49)]
5	CO_2Me	E	**92**[a], **75**[b] [0/100 (98/2)]	**55** [0/100 (10/90)]	**70** [0/100 (7/93)]
6	CO_2tBu	E	**55**[b] [0/100 (97/3)]	**32** [0/100 (8/92)]	**87** [0/100 (7/93)]
7	$CONMe_2$	E	**53**[b] [(0/100 (99/1)]	**14** [0/100 (8/92)]	**81** [0/100 (4/96)]
8	COtBu	E	**82**[a] [0/100 (93/7)]	**84** [0/100 (6/94)]	**52** [0/100 (12/88)]

* Prepared on reaction of: (a) 1.6 $Ph_2S^+CHMe_2$, BF_4^-, 1.5 LDA, 1.5 CH_2Cl_2, DME, -78°C, 0,25h then **1**, -78°C to -50°C, 2h; (b) 1.6 $Ph_2S^+CHMe_2$, BF_4^-, 1,5 PhLi, THF, -78°C, 0,25h then **1**, -78°C, 2h; (c) 1,6 $Ph_3P^+CHMe_2$, I^-, 1.5 nBuLi, THF 0°C, 0.2h then **1** 20°C, 2h (d) 1.6 $(Me_2CH)_2S(O)(NTs)$, 1.5 nBuLi, THF, -78°C to 20°C, 0.5h.

Table

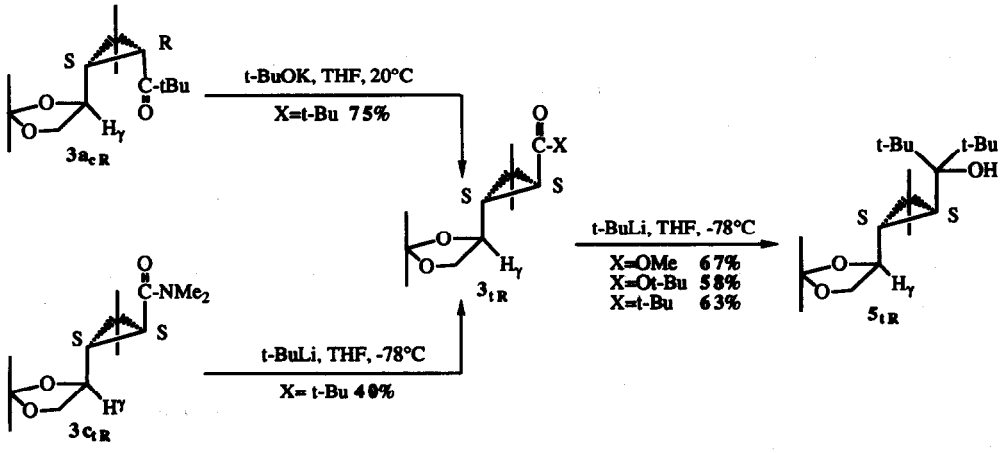
As general trends (**i**) Z-α,β-unsaturated carbonyl compounds led, except rare cases, to higher yield in cyclopropanes than their E-analogues (table compare entries 1 to 4 to entries 5 to 8) (**ii**) amides proved to be the least reactive members of the series (table, entries 3 and 7). They do not react at low temperature with isopropylidenediphenylsulfurane and the temperature must be carefully adjusted in order to prevent the decomposition of the ylide. This has been achieved by slowly raising the temperature to - 40°C. We thought that t-butyl esters would react more efficiently that their methyl analogue due to the higher stability of the resulting enolate intermediate. They in fact do not offer a definite advantage over their methyl analogue when reacted with the sulfurane or phosphorane but proved to be the best substrates towards 2-lithio-2-propyl N-tosyl isopropyl sulfoximine. Z- and E-t-butyl ketones react highly chemoselectively with all the ylides used and produce the corresponding cyclopropane, resulting from an attack on their C,C double bond, rather than an epoxide or an olefin resulting from reaction on the keto-group. The reaction of both Z- and E-stereoisomers with the sulfur ylide was particularly efficient as it is also the case of E-stereoisomer and the phosphonium ylide. It is interesting to notice that this compound was, amongst the various substrates possessing the E-

stereochemistry, the one who produced by far the best yield of cyclopropane derivative when reacted with the phosphonium ylide (table, compare entry 8 to entries 5 to 7).

The results concerning the relative stereochemistry on the cyclopropane ring described in this work, are in complete agreement with those disclosed in our previous work (cis-cyclopropane derivatives from the Z-γ-alkoxy-α,β-unsaturated carbonyl compounds and isopropylidenediphenylsulfurane; trans-cyclopropane derivatives indistinctly from Z- or E-α,β-unsaturated carbonyl compounds) and is independent of the nature of the electron withdrawing group. This stereochemical control is very high in almost all the cases (de 88 to 99%) except when the Z-α,β-unsaturated t-butyl ester is reacted with 2-lithio-2-propyl N-tosyl isopropyl sulfoximine (de 68%).

Very high facial stereoselection is achieved in almost all the cases. The reaction occurred by the Re face with all the substrates and reagents (84<de<90%) at the exclusion of E-α,β-unsaturated carbonyl compounds and isopropylidenetriphenylphosphorane or 2-lithio-2-propyl N-tosyl isopropyl sulfoximine (74<de<96%) which instead reacted by the Si face. The poorest stereocontrol has been observed with the Z-t-butyl ketone and 2-lithio-2-propyl N-tosyl isopropyl sulfoximine (de < 2) and might be the result of partial Z/E isomerisation of the starting material prior its cyclopropanation. We have in fact observed that, possibly due to the reversibility of the addition step, substantial amounts of more stable E-stereoisomer are present when these reactions are quenched prior completion.

The relative stereochemistry of the different cyclopropane derivatives **3** disclosed in this work has been assigned on the basis of their ^{1}H [27] and ^{13}C NMR. We have furthermore confirmed these assignments in the case of the t-butyl cyclopropyl ketone **3d** by performing the cis/trans $\mathbf{3d_{cR}/3d_{tR}}$ isomerisation (3 equiv. t-BuOK, THF, 20°C, 1h, 75%). The absolute stereochemistry of each stereoisomer of the trans series has been attributed on basis of chemical correlations of the di-ter-butyl alcohol $\mathbf{5_{tR}}$ derived from the t-butyl ester $\mathbf{3b_{tR}}$ and the t-butyl ketone $\mathbf{3d_{tR}}$ obtained by cyclopropanation of the corresponding α,β-unsaturated carbonyl compound (2 equiv. or 1 equiv. t-BuLi, THF, -78°C to 20°C, 0.5h, 58 or 63% respectively, scheme 2) with the one derived from the known methyl cyclopropane carboxylate $\mathbf{3a_{tR}}$ (2 equiv. t-BuLi, THF, -78°C to 20°C, 0.5h, 67%, Scheme 2).[3-5] The t-butyl ketone $\mathbf{3d_{tR}}$ has been also prepared from the N,N-dimethylamide $\mathbf{3c_{tR}}$ (1 equiv. t-BuLi, THF, -78°C to 20°C, 0.5h, 40%, Scheme 2).



Scheme 2

We are now trying to extend this reaction to the methylenation of these γ-alkoxy-α,β-unsaturated carbonyl compounds.

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27 The γ-hydrogens possess a downfield (0,5 to 1,0 ppm) chemical shift for the cis- compared to the trans cyclopropane derivatives.

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