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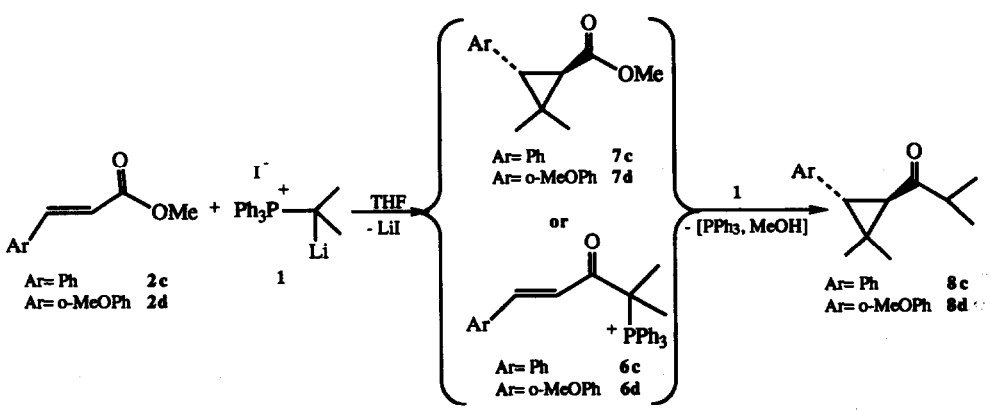
On the Reactivity of i-Propylidenetriphenylphosphorane with some α, β-Unsaturated Esters, -Amides and Acyl Chlorides

Alain Krief * and Philippe Dubois [1]

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

Abstract: Isopropylidenetriphenylphosphorane allows the cyclopropanation of α,β-unsaturated carbonyl compounds including α,β-unsaturated esters, -ketones, -amides and -acid chlorides. Concomitant reaction on the carbonyl group of methyl cinnamates and cinnamoyl chlorides leading to cyclopropyl ketones has been observed.

In the course of a work directed towards the synthesis of chrysanthemic esters,[1-7] we had the occasion to react [1] isopropylidenetriphenylphosphorane **1**, generated from the corresponding phosphonium iodide and n-BuLi, with methyl crotonate **2a**, -hexenoate **2b** and -cinnamate **2c** used as models. Whereas the former derivative did not produce a definite product, probably due to a competing enolisation reaction, the second led chemoselectively to the corresponding methyl gem-dimethyl cyclopropane carboxylate **7b** in moderate yield and the later surprisingly delivered a mixture of the expected methyl cyclopropane carboxylate **7c** beside substantial amounts of (2,2-dimethyl-3-phenyl)cyclopropyl isopropyl ketone **8c** (Schemes 1, 2 entries 3, 4). This type of reactivity seems to be general for those α,β-unsaturated methyl esters bearing an aryl group at the β-site since we observed similar results from the o-methoxy phenyl substituted cinnamate **2d** (Scheme 2 entries 5)



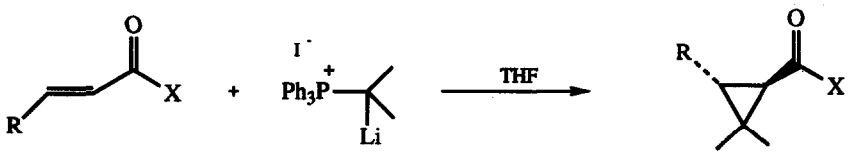
Scheme 1

These ketones might arise from the reaction of isopropylidenetriphenylphosphorane **1** (i) on the carbonyl group of methyl cinnamates **2c**, **2d** prior to their cyclopropanation or (ii) on the carbonyl group of methyl 2-aryl-

3,3-dimethylcylopropane carboxylates **7c**, **7d** just after the cyclopropanation has taken place. We have ruled out the second alternative since we found that isopropylidenetriphenylphosphorane **1** does not react further with methyl 2-phenyl-3,3-dimethyl carboxylate **7c** even under forced conditions.

The ester **7c** required for this control experiment cannot be obtained directly from the corresponding methyl cinnamate **2c** and the phosphonium ylide **1** since we have been unable to separate it, by distillation or chromatography on SiO_2, from the cyclopropyl ketone **8c** concomitantly produced. We have however found that this ester can be chemoselectively produced, after trans-esterification, from the same ylide and isopropyl cinnamate **2e** whose carbonyl group is more hindered than the previous one's (Scheme 2, entry 6).

These results led us to investigate the reaction of isopropylidenetriphenylphosphorane **1** with 4-methyl-1-phenyl-penten-3-one **3c** (Scheme 2, entry 7),[8] α,β-unsaturated N,N-dimethyl amides **4** including the cinnamoyl amide **4a** (Scheme 2, entries 8-13), and cinnamoyl chlorides **5c** and **5f** (Scheme 2, entries 14, 15), whose electrophilicity as well as steric hindrance around the carbonyl group differ from those of the esters described above.



2-5 **1** **7-10**

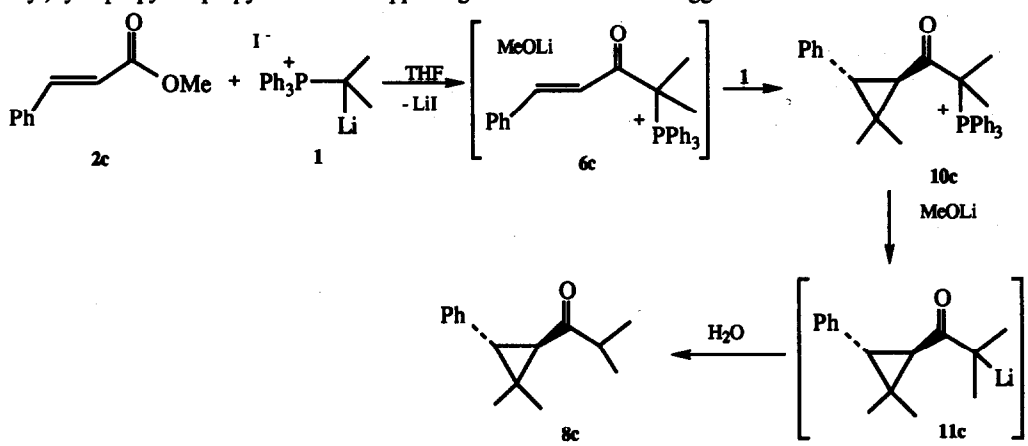
Scheme 2

Entry	X	R	Starting material	Experimental conditions (equiv.)	Yield % in **7-10** (X)
1	OMe	Me	**2a**	1 (1.1), THF, -78°C, 1h, 20°C, 1.5h	traces , **7a** (OMe)
2	OMe	Pr	**2b**	1 (1.1), THF, -78°C, 5h, 20°C, 3.5h	46%, **7b** (OMe)
3	OMe	Ph	**2c**	1 (1.1), THF, 0°C, 1h, 20°C, 3.5h	31%, **7c** (OMe); 7%, **8c** (i-Pr)
4	OMe	Ph	**2c**	1 (1.3), THF, 0°C, 1h, 20°C, 5h	45%, **7c** (OMe); 21%, **8c** (i-Pr)
5	OMe	o-MeO-Ph	**2d**	1 (1.3), THF, 0°C, 1h, 20°C, 12h	33%, **7d** (OMe); 12%, **8d** (i-Pr)
6	Oi-Pr	Ph	**2e**	1 (1.3), THF, 0°C, 1h, 20°C, 2.4h	70%, **7e**(O-i-Pr)
7	i-Pr	Ph	**3c**	1 (1.2), THF, 0°C, 1h, 20°C, 2h	67%, **8c** (i-Pr)
8	NMe_2	Me	**4a**	1 (1.1), THF, 0°C, 1h, 20°C, 4h	0%, **9a** (NMe_2)
9	NMe_2	Pr	**4b**	1 (1.2), THF, 20°C, 6.5h	20%, **9b** (NMe_2)
10	NMe_2	Pr	**4b**	1 (2), THF, 20°C, 1h, 70°C, 3h	60%, **9b** (NMe_2)
11	NMe_2	Ph	**4c**	1 (1.3), THF, 0°C, 1h, 20°C, 3.5h	38%, **9c** (NMe_2)
12	NMe_2	Ph	**4c**	1 (1.3), THF, 0°C, 1h, 20°C, 48h	48%, **9c** (NMe_2)
13	NMe_2	Ph	**4c**	1 (2.4), THF, 0°C, 1h, 20°C, 4h	67%, **9c** (NMe_2)
14	Cl	Ph	**5c**	1 (2.4), THF, 0°C, 1h, 20°C, 4h	30%, **8c** (i-Pr); 63%, **10c** ($C(Me)_2{}^+PPh_3$), I^-
15	Cl	p-NO_2-Ph	**5f**	1 (2.4), THF, 0°C, 1h, 20°C, 4h	46%, **8f** (i-Pr); 46%, **10f** ($C(Me)_2{}^+PPh_3$), I^-

The ketone **3c** reacted efficiently (Scheme 2, entry 7) whereas the amides **4** proved, as expected, much less reactive and required quite drastic conditions for successful cyclopropanation (Scheme 2, entries 9-13). Both

reactions were completely chemoselective leading to an analytically pure authentic sample of (2,2-dimethyl-3-phenyl)cyclopropyl isopropyl ketone **8c** (Scheme 2, entries 7) and to the cyclopropane carboxamides **9b** and **9c** (Scheme 2, entries 10;13) in reasonably good yields. Again the crotonic acid derivative **4a** did not deliver the corresponding cyclopropane derivative (Scheme 2, entry 8 compare to entry 1).

The case of cinnamoyl chlorides **5c** and **5f** (Scheme 2, entries 14 and 15) required further comments since these compounds do not lead to 2,2-dimethyl-3-aryl cyclopropane carboxylic acid chlorides nor to the corresponding acids (by hydrolysis) but provided instead a readily separable mixture of the (2,2-dimethyl-3-phenyl)cyclopropyl isopropyl ketones **8c** and **8f** and of (2,2-dimethyl-3-phenyl)cyclopropyl 2-(2-triphenylphosphino)propyl ketones **10c** and **10f** which are expected to be their direct precursors. Treatment of the phosphonium salt **10c** with lithium methylate (1.5 equiv., MeOH, 20°C, 48h), the by-product expected to be formed concomitantly to (2,2-dimethyl-3-phenyl)cyclopropyl 2-(2-triphenylphosphino)propyl ketone **10c** on reaction of isopropylidenetriphenylphosphorane with methyl cinnamate, led to the formation of (2,2-dimethyl-3-phenyl)cyclopropyl isopropyl ketone **8c** supporting thus the mechanism suggested in the Scheme 3.



Scheme 3

To our knowledge they are only few reports dealing with the reaction of phosphonium ylides with acid chlorides or carboxamides and even fewer involve their α,β-unsaturated analogues.[9] The reaction we have reported on methyl cinnamate does not seem to be precedented.[2-7,9-13] In fact if reactions of phosphonium ylides on the carbonyl group of carboxylic esters or acid chlorides have been from time to time reported,[9] they all deal with ylides bearing at least one hydrogen on the carbanionic center and the resulting β-keto phosphonium salts, which possess particularly acidic hydrogens suffer from a metallation reaction rather than from the reaction reported here. Work is now in progress in order to use this novel reaction for the regioselective synthesis of highly substituted enolates.

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