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Syntheses of pentafulvenes from 4-alkylidenecyclopentenones

Frédéric Antras, Mohammed Ahmar and Bernard Cazes*

Laboratoire de Chimie Organique I, associé au CNRS, Université Claude Bernard-Lyon, Bât. CPE-Lyon,
43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France

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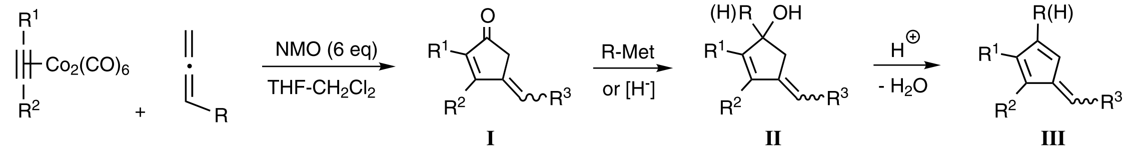
Abstract—An efficient synthesis of polysubstituted pentafulvenes from 4-alkylidenecyclopentenones is reported via a two-step procedure consisting of addition of an organometallic reagent (or reduction) followed by dehydration. © 2002 Elsevier Science Ltd. All rights reserved.

4-Alkylidene-2-cyclopentenones **I** are relatively little known compounds, presumably because of difficult or unselective preparation.[1,2] We recently developed a straightforward synthesis of these cyclopentenones via the *N*-methylmorpholine oxide (NMO) initiated Pauson–Khand reaction of alkynes with allenic compounds (Scheme 1).[3] This route was in most cases highly regioselective[4] and should be considered as a rather general route to 4-alkylidene-2-cyclopentenones **I** as the experimental conditions are compatible with a large number of functionalities.[5,6]

These cyclopentenones **I** might be appropriate starting materials for the synthesis of pentafulvenes **III** via the dienic alcohols **II** obtained by the addition of organometallic reagents or the reduction of ketones **I**. This strategy has been shortly described by Martin et al. who obtained some few pentafulvenes by the slow addition of an 4-alkylidenecyclopentenone **I** to an ethereal solution of methyl or phenyllithium (1.2 equiv.) at −70°C, followed by an acidic work-up which realized the dehydration of the intermediate alcohol **II**.[7]

However, the yields of fulvenes **III** were not clearly mentioned and the reactions with various lithium compounds turned out to be difficult to reproduce in our hands, because of the easy enolization of the 4-alkylidenecyclopentenones. Indeed, the reaction of ketones **1c** with *n*BuLi (1.2 equiv.) in ether at −78°C followed by an acidic work-up gave only the recovered ketone **1c**. On the other hand a similar addition at −78°C followed by quenching with diethylchlorophosphate gave the enol phosphate **3** (20%) and very small amounts of the phosphate **4** (5%) together with the recovered ketone **1c** (Scheme 2). We report here on more effective conditions for the 1,2-addition of an organometallic species to 4-alkylidenecyclopentenones **I**, as well as on the reduction of the keto group of these compounds.

We observed that the reaction of lithium reagents with the cyclopentenones **1** was more efficient in ether at 0–20°C and gave the very unstable[7] tertiary dienic alcohols **5**. Then, these crude alcohols **5** were immediately treated with 2–4% M *p*-toluenesulfonic acid or with $ZnBr_2$ (1 equiv.) in petroleum ether at room temperature for 15–30 min. Both conditions gave pentafulvenes **6** in similar yields. The yields depended dramatically on the number of equivalents of the added organometallic compound (results summarized in Table 1). Indeed, the addition of butyllithium (1.2 equiv.) to cyclopentenone **1a** gave the pentafulvene **6a** with a low



Scheme 1.

Keywords: cyclopentenones; alkyllithium; Grignard reagents; addition reactions; fulvenes.

* Corresponding author. Tel.: +33 4.72.44.85.39; fax: +33 4.72.43.12.14; e-mail: cazes@univ-lyon1.fr

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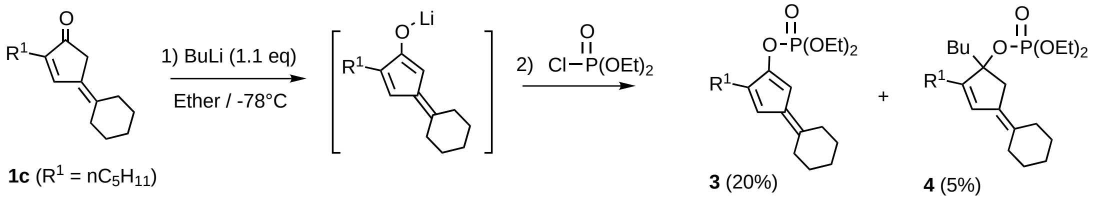
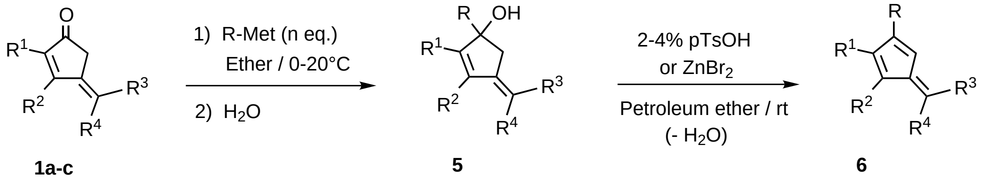


Scheme 2.

Table 1. Synthesis of pentafulvenes **6** via addition of organometallic reagents to 4-alkylidenecyclopentenone/dehydration



Entry	Cyclopentenone **1**	R^1	R^2	R^3	R^4	R-Met	No. equiv.	Pentafulvene **6**	Yield (%)[a] **6**
1	**1a**	nC_3H_7	nC_3H_7	nC_6H_{13}	H	BuLi	1.2	**6a**	28
2	**1a**	nC_3H_7	nC_3H_7	nC_6H_{13}	H	BuLi	2.5	**6a**	38
3	**1b**	CH_3	CH_3	$-(CH_2)_5-$		BuLi	2.5	**6b**	31
4	**1b**	CH_3	CH_3	$-(CH_2)_5-$		BuLi	5	**6b**	60
5	**1b**	CH_3	CH_3	$-(CH_2)_5-$		BuLi	10	**6b**	77
6	**1b**	CH_3	CH_3	$-(CH_2)_5-$		PhLi	5	**6c**	78
7	**1b**	CH_3	CH_3	$-(CH_2)_5-$		PhLi	10	**6c**	93
8	**1c**	nC_5H_{11}	H	$-(CH_2)_5-$		MeMgBr	1.2	**6d**	35
9	**1c**	nC_5H_{11}	H	$-(CH_2)_5-$		MeMgBr	2.5	**6d**	65
10	**1c**	nC_5H_{11}	H	$-(CH_2)_5-$		BuMgBr	2.5	**6e**	46
11	**1b**	CH_3	CH_3	$-(CH_2)_5-$		MeMgBr	2.5	**6f**	72
12	**1b**	CH_3	CH_3	$-(CH_2)_5-$		PhMgBr	5	**6g**	60
13	**1b**	CH_3	CH_3	$-(CH_2)_5-$		PhMgBr	10	**6g**	83
14	**1b**	CH_3	CH_3	$-(CH_2)_5-$		CyMgBr	10	**6h**	86

[a] Yield of purified products **6** after a short chromatography on alumina.

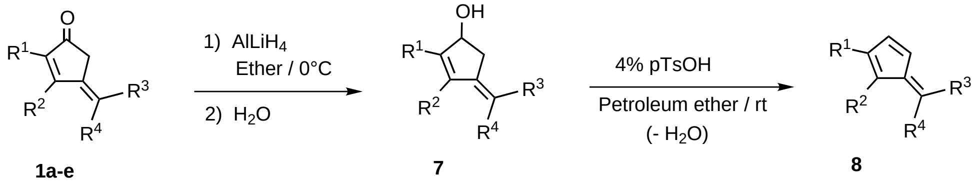
28% yield (entry 1) while the yield increased to 38% by using 2.5 equiv. (entry 2). Similar results were observed with the addition of BuLi and PhLi to ketone **1b** (entries 3–7). Yields up to 77–93% were obtained when 10 equiv. of the organolithium were used (entries 5 and 7). Thus, the use of a large excess of the lithium reagents is necessary to promote the 1,2-addition to the carbonyl group of cyclopentenones **1** over the enolate anion formation. Aggregation phenomena between solvent,[8] Lewis bases[9] or lithium alkoxides[10] and the alkyllithium compounds may be taken into account to explain this chemoselectivity.[11] Indeed, more aggregated reagents have been pointed out to favour the 1,2-addition.[9]

The addition of organomagnesium compounds to cyclopentenones **1** were very similar.[12] We observed the same increase of the yields for the overall transformation when an excess of the Grignard reagent was used (entries 8–14). Yields as high as 85% were obtained with the addition of 10 equiv. (entries 13 and 14).

The reduction of cyclopentenones **1a**–**e** was classically carried out with 1 equiv. $LiAlH_4$ in ether at 0°C followed by quenching with aqueous NaOH (Table 2). The secondary dienic alcohols **7** were considerably more stable than the corresponding tertiary ones **5**, as spectroscopic NMR analysis was feasible without the in situ dehydration to fulvene **8**. This last transformation was easily realized in acidic conditions and gave pentafulvenes **8** with satisfactory yields (50–80%).

In summary, we have demonstrated that the 1,2-addition of organolithium and organomagnesium compounds to 4-alkylidenecyclopentenones requires a large excess of these reagents to achieve a satisfactory conversion of these peculiar cyclopentenones, because of their easy enolization. Thus, the two-step procedure for addition of an organometallic reagent or reduction followed by dehydration constitutes an efficient synthesis of polysubstituted pentafulvenes from 4-alkylidenecyclopentenones. These methods offer the advantage of producing regioselectively substituted pentafulvenes which are versatile synthetic intermediates.[13]

Table 2. Synthesis of pentafulvenes **8** via reduction of 4-alkylidenecyclopentenone/dehydration



Cyclopentenone **1**	R^1	R^2	R^3	R^4	Yield (%)[a] alcohol **7**	Yield (%)[b] pentafulvene **8**
1a	nC$_3$H$_7$	nC$_3$H$_7$	nC$_6$H$_{13}$	H	97	53
1b	CH$_3$	CH$_3$	-(CH$_2$)$_5$-		95	68
1c	nC$_3$H$_7$	H	-(CH$_2$)$_5$-		99	82
1d	nC$_3$H$_7$	nC$_3$H$_7$	-(CH$_2$)$_5$-		99	62
1e	Ph	H	-(CH$_2$)$_5$-		94	48

[a] Yield of crude alcohols.

[b] Yield of purified products after short chromatography on alumina.

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12. **Typical procedure** (Table 1, entry 11): To methylmagnesium bromide (1.28 mmol, 2.5 equiv.) in Et$_2$O (5 mL) at 0°C, a solution of 4-alkylidenecyclopentenone **1b** (97 mg, 0.51 mmol) in Et$_2$O (4 mL) was added dropwise. After the reaction was completed, the mixture was quenched with a saturated aqueous NH$_4$Cl solution (10 mL) and extracted with ether (2×10 mL). The combined organic phases were dried over anhydrous MgSO$_4$, filtered and concentrated under vacuo. The mixture was diluted with petroleum ether (4 mL), and pTsOH (0.2N THF solution, 50 μL, 0.02 equiv.) was added. After stirring for 10 min., a short chromatography on alumina (Grad III, PE as eluent) afforded 6,6′-pentamethylene-1,2,3-trimethylpentafulvene **6f** (70 mg, 72%) as a yellow oil. TLC (Al$_2$O$_3$, PE): R_f=0.74. IR (neat, cm^{-1}): 2960, 2920, 2860, 1620, 1450, 1380, 1340, 1080, 730. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.69 (m, 6H), 1.89 (s, 3H), 1.97 (s, 3H), 2.16 (s, 3H), 2.57 (t, ^3J=6.6 Hz, 2H), 2.74 (t, ^3J=6.6 Hz, 2H), 6.18 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 11.0, 14.2 and 15.4 (3×CH$_3$); 26.7, 28.6, 29.2, 32.0 and 34.8 (5×CH$_2$); 115.7 (C_4); 125.8 (C_1); 137.8 (C_5); 139.6 (C_2); 140.7 (C_3); 152.2 (C_6).
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