Tetrahedron Vol. 46, No. 21, pp. 7497-7508, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

Nitrodienic-like Reactivity of 2-Nitrofuran with Organometallic Reagents: One-step Synthesis of Alkylfuranones.

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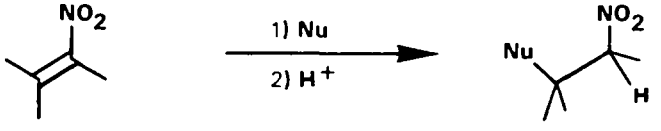
(*Received in USA* 14 *February* 1990)

Abstract: *2-Nitrofuran reacts with Grignard, alkyllithium, dialkylcadmium and heterocuprate reagents affording mixtures of 5-alkyl- and 3-alkyl-2-furanones.*

The conjugate addition of nucleophiles to nitro olefins (**1**) is one of the most useful synthetic pathways to obtain saturated nitro compounds (**2**) which are versatile intermediates in organic synthesis[1] (Scheme 1). In particular, the reaction of **1** with carbon-centered nucleophiles represents a versatile method for new C-C bond formation.[1]

Scheme 1



1 **2**

This attractive opportunity has for a long time been limited to the use of stabilized carbanions because initial work on the conjugate addition of alkyl Grignard reagents to nitro olefins reported the occurrence of competing 1,2-addition reactions and polymerization of the substrate.[2] Successively a number of lithium,[3] magnesium,[3g-i,4] and cadmium[5] organometallics and organocuprates[6] have been reported to react with nitro olefins affording addition products in moderate to satisfactory yields. Recent work has also stressed that the 1,4-addition of aryl or allyl groups can

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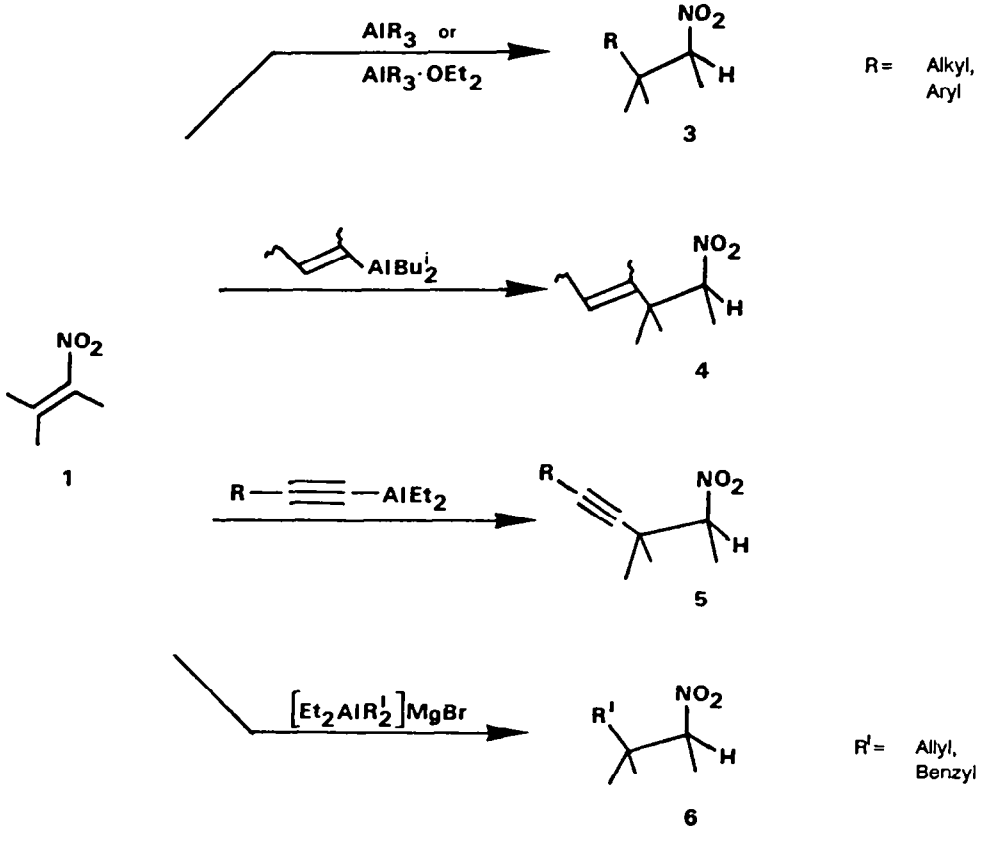
be performed by using arylmagnesium halides[7] and allylsilanes[8] or stannanes.[9] Moreover, highly functionalized nitroalkanes can be prepared in very good yields by reacting 1 with the zinc-copper reagents RCu(CN)ZnI.[10]

In this context we showed that organoaluminum compounds reacted with nitro olefins under mild experimental conditions and, depending on the nature of the organometallic reagent employed, the transfer of either alkyl,[11] alkenyl,[12] alkynyl,[13] or allyl[13] groups took place to produce the corresponding derivatives 3-6 in very good yields (Scheme 2).

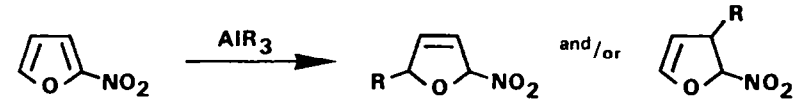
Scheme 2



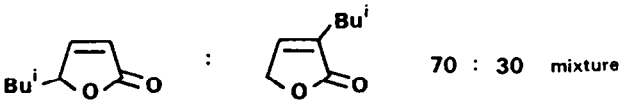
The most striking features of the described reaction are the observed chemo- and regioselectivities that are not found in the reactions of such organometallic reagents with other α,β-unsaturated systems.[14] To verify whether a similar selectivity could also be shown by a nitro dienic-like

system, AlR_3 was reacted with 2-nitrofuran (**7**), from which either the 1,6- or 1,4-addition products (**8** and **9** respectively, Scheme 3) could arise.

Scheme 3



7 **8** **9**



10 **11**

Preliminary results[15] showed that the reactivity of **7** towards triisobutylaluminum was quite different from that of nitro olefins **1**, in fact 2-nitrofuran had to be reacted at very low temperature (-95°C) to avoid its extensive degradation. Moreover, the alkylated nitro compounds **8** or **9** were not recovered even when mild hydrolysis conditions (-10°C, 0.3 N HCl) were adopted. In all cases only the butenolides **10** and **11**, were isolated from the reaction mixture (Scheme 3).

Under similar experimental conditions, 5-methyl-2-nitrofuran (**12**) selectively yielded the 1,4-addition products **13a-c**[15] (Scheme 4).

Scheme 4

12 **13a-c**

RM = a) $AlEt_3$
b) $AlBu^i_3$
c) $[Et_2Al\,All_2]\,MgBr$

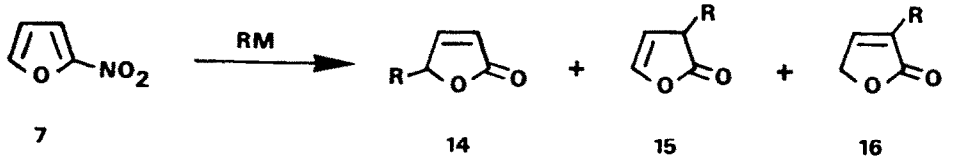
These findings appeared very interesting considering that alkylfuranones and, in particular, 5-alkyl-2(5H)-furanones are often both biologically active natural compounds[16] and useful intermediates in organic

synthesis.[17]

Unfortunately the preparation of ether free trialkylaluminum reagents is generally troublesome and time consuming;[14a] moreover, while the reaction of trialkylaluminum etherates with nitro olefins **1** gave very good results,[11] the corresponding reaction of **7** afforded only tarry products.[15] Owing to this limitation, the reaction of **7** with some widely employed organometallic reagents was then studied. Here we report the results obtained with some magnesium, lithium, cadmium and copper derivatives.

Results and Discussion. The reaction of 2-nitrofuran (**7**) with RMgX (1.2 equiv.) was first carried out at -90°C (Scheme 3). Surprisingly, in this case only a moderate conversion to products (ca. 50%) was observed.

Scheme 5



7 **14** **15** **16**

R= a) *n.* Butyl; b) *n.* Octyl; c) *i.* Propyl; d) *c.* Hexyl; e) *t.* Butyl

Further experimental work showed that an excess (RMgX / **7** = 2.5, Table, Procedure A) of organometallic reagent brought about the complete conversion of the substrate into mixtures of the alkylfuranones **14-16** (Scheme 5). These produts were isolated in ca. 50% yields. When the organometallic reagent was added to an ethereal solution of **7** (Table, Procedure B), only a slight excess of the magnesium derivative was necessary to completely convert **7** into mixtures of furanones **14-16** in 60-75% yields.

The pure alkylfuranones **14-16** were obtained by flash^@tography, although it has been reported[18] that this technique caused partial decomposition of such substances.

The isolation of **16** was particularly difficult since this product, characterized by a higher Rf than **14** and **15**, decomposed during the purification process. Therefore only small amounts of **16** were obtained, although GLC analysis of the crude reaction mixture indicated that **16** was formed in equivalent amounts to **14** and **15**.

The reaction showed different characteristics depending on the nature of the Grignard reagent used. When phenylmagnesium bromide was used, only

Table

Product distributions in the reactions of **7** with organometallic reagents.[a]

Run	RM	Procedure[c]	Product Distribution %[b] **14**	**15**	**16**	1,6 / 1,4 Addition
1	*n*-BuMgBr	A	34(22)	31(6)	35(9)	34 / 66
2	*i*-PrMgBr	A	47(23)	53(17)	-	47 / 53
3	*c*-HexylMgBr	A	67(26)	-	33(10)	67 / 33
4	*n*-BuMgBr	B	52(42)	38(23)	10	52 / 48
5	*n*-BuMgBr	B[d]	49(25)	48(22)	3	49 / 51
6	*n*-OctylMgCl	B	71(39)	-	29[e]	71 / 29
7	*i*-PrMgBr	B	43(28)	26(12)	31(8)	43 / 57
8	*t*-BuMgCl	B	73(22)	27(5)	-	73 / 27
9	*n*-BuLi	B	57(24)	-	43(26)	57 / 43
10	*t*-BuLi	B	100(50)	-	-	100 / 0
11	*n*-Bu_2Cd	A	60(27)	40(18)	-	60 / 40
12	(*n*-BuCuBr)MgBr·LiBr	A[d,f]	47	10	43	47 / 53
13	(*i*-PrCuBr)MgBr·LiBr	A[d]	34	13	53	34 / 66
14	*n*-$BuCuMgBr_2$	A[d]	43(15)	8	49(17)	43 / 57

[a] All the reactions were performed in ether unless otherwise stated; [b] Glc evaluation (⩽5% unknown products were rejected), the number in parentheses are isolated yields of chemically pure products; [c] "A": **7** added to 2.2 molar equivalents of RM; "B": 1.2 molar equivalents of RM added to **7**; [d] Reaction performed in THF; [e] See ref. 19; [f] The isolated yield of the purified **14**, **15**, **16** mixture was 32%.

diphenyl[20] and the unreacted precursor were recovered. Allylmagnesium bromide gave a complex reaction mixture in which only a small amount of 5-allyl-2(5H)-furanone (**14f**)[21] was detected. In this case repeated flash-chromatography gave a chemically pure sample of **14f** (6%).

Since the reaction of nitroarenes with allyl Grignard reagents, followed by reductive work-up,[22] has been reported to give N-allylated products, the reaction of **7** with allylmagnesium bromide was undertaken. In this case, also, a very complex reaction mixture was obtained and no N-allylated derivatives were detected.

The results obtained in the reactions of **7** with RMgX (Table, runs 1-8) generally showed a low regioselectivity (1,6 vs 1,4 addition). In further experiments **7** was reacted with alkyllithium, dialkylcadmium and dialkylcuprate reagents (Table, runs 9-14), in order to test whether the regioselectivity could be affected by the nature of the counter cation.

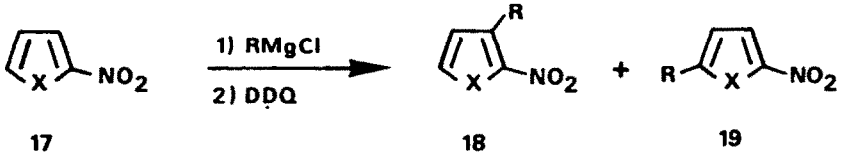
Only by using *t*-butyllithium (Table, run 10) was the regioselectivity

improved. Other alkyllithium reagents and dibutylcadmium afforded the adducts **14-16** in yields comparable with those obtained with the corresponding Grignard reagents. Both homo- and heterocuprates gave lower yields of the furanones adducts (Table).

The reported data[23] showed a remarkable difference between the reactivity of 2-nitrofuran and those of 2-nitrothiophene and 1-alkyl-2-nitropyrroles. In fact, while the reaction of both 2-nitrothiophene and 1-alkyl-2-nitropyrroles with RMgX, followed by an oxidative work-up, gave mixtures of the corresponding alkylated nitro derivatives **18** and **19** (Scheme 6), the same reaction on 2-nitrofuran failed.[23]

These results, together with our findings, clearly show that 2-nitrofuran **7** beaves as a nitrodiene in its reaction with organometallic derivatives. In contrast, 2-nitrothiofene and 1-alkyl-2-nitropyrroles (**17**) react as heteroaromatic substances (Scheme 6).

Scheme 6



17 **18** **19**

X = S or NR'

Conclusions. Alkylfuranones can be obtained, in one step, starting from 2-nitrofuran and the commonly used Grignard or alkyllithium reagents, reagents. Although the regioselectivity of the reaction is rather low, 5-alkyl-2(5H)-furanones **14** can be obtained in 25-50% isolated yields. Since these compounds are widely distributed in nature and play an important role in organic synthesis, the described methodology provides a new synthetic approach to useful intermediates such as 5-octyl-2(5H)-furanone **14b**.[24]

Experimental Section

Materials and Instrumentation. All the reactions were carried out in dry apparatus under argon. Tetrahydrofuran and diethyl ether were purified by standard methods and distilled from $LiAlH_4$ before use. Ethereal solutions (0.5-1.5 M) of *n*-butylmagnesium bromide, octylmagnesium bromide,

t-butylmagnesium bromide, *i*-propylmagnesium bromide, cyclohexylmagnesium bromide, phenylmagnesium bromide and allylmagnesium bromide were prepared by standard procedures; hexane solutions (2.5 M) of *n*-butyl- and *t*-butyllithium are commercially available (Aldrich). Diethyl ether solutions of dibutylcadmium[25] and tetrahydrofuran solutions of the (RCuBr)MgBr·LiBr[26] and *n*-BuCu·$MgBr_2$[27] were prepared according to reported procedures.

GLC analyses were performed on a Perkin Elmer 8500 instrument (DB1, 12m x 0.22 mm capillary column) equipped with a flame ionization detector and using He as the carrier gas. IR spectra (ν cm^{-1}) were obtained on a Perkin Elmer FT IR 1750 spectrophotometer using liquid films (20 μm). ^1H NMR and ^{13}C NMR were recorded on a Varian Gemini 200 (200 and 50 MHz respectively) spectrometer. All NMR data were obtained in $CDCl_3$ solutions, and chemical shifts (δ ppm) are referred to tetramethylsilane (^1H NMR) or $CDCl_3$ (^{13}C NMR) as internal reference. Mass spectra (m/z, relative intensity) were taken on a VG-Analytical 7070 GC-MS instrument. All the isolated furanones **14**, **15** and **16** gave satisfactory elemental analyses (±0.4%). Analytical TLC were performed on silica gel (Merck, SiO_2 60). The crude mixtures of 3-alkyl- and 5-alkyl-2-furanones (**14-16a-e**) were purified by flash chromatography (Merck, SiO_2 60, 230-400 mesh) employing the following eluting mixtures:
[R = *n*-Butyl (**a**)] ethyl acetate/petroleum ether 15/85; [R = *n*-octyl (**b**)], acetone/petroleum ether 30/70; [R = *i*-propyl (**c**)] acetone/petroleum ether 8/92; [R = *c*-hexyl(**d**)] acetone/ethyl acetate 20/80; [R = *t*-butyl (**e**)] ethyl acetate/petroleum ether 15/85.

Reactions of 2-Nitrofuran with RMgBr. Procedure A. An ethereal solution of **7** (3 g, 27 mmol) was added dropwise to a stirred solution of the Grignard reagent (60 mmol), cooled to -90°C . After stirring for further 30 min at -90°C, the temperature was slowly raised to *ca.* -50°C and the reaction mixture was rapidly poured into a flask containing 300 mL of a cooled (*ca.* -10°C) 0.2 N HCl solution saturated with NaCl and ether (100 mL). The organic products were extracted into ether (4x150 mL) and dried over Na_2SO_4. The solvent was evaporated (r.t., 20 mmHg) to give crude products **14**, **15** and **16** which were in turn purified by flash chromatography.

Reaction of 2-Nitrofuran with *n*-Bu_2Cd. Procedure A. An ethereal solution (20 mL) of **7** (1.80 g, 16 mmol) was added dropwise to a cooled (0°C) freshly prepared suspension of di-*n*-butylcadmium (42 mmol) in the same solvent (60 mL). The mixture was stirred 24 h at room temperature and then worked-up as described above.

Reactions of 2-Nitrofuran with (RCuBr)MgBr·LiBr or *n*-BuCu·MgBr₂. Procedure A. A THF solution (50 mL) of **7** (2.0 g, 18 mmol) was added dropwise to a cooled (-80°C) suspension of the cuprate reagent (45 mmol) in the same solvent. The temperature was slowly raised to -50°C and, after an additional 40 min, the reaction mixture was worked-up as described for the reactions using Grignard reagents.

Reactions of 2-Nitrofuran with RMgBr or RLi. Procedure B. A solution of the organometallic reagent (31 mmol) was added dropwise to a stirred and cooled (-90°C) solution of 2-nitrofuran (3 g, 27 mmol) in diethyl ether (90 mL). After stirring for additional 30 min. at -90°C, the temperature was slowly raised to ca. -50°C (3 h) and the mixture hydrolyzed and worked-up as described above.

The isolated products showed:

14a: ^{1}H NMR, 7.48 (dd, 1H, J=5.7, J=1.4 Hz), 6.12 (dd, 1H, J=5.7, J=1.9 Hz), 5.05 (tdd, 1H, J=7.2, J=5.6, J=1.7 Hz), 2.00-1.50 (m, 2H), 1.50-1.00 (m, 4H), 0.93 (t, 3H, J=6.7 Hz); ^{13}C NMR, 173.34, 156.51, 121.51, 83.36, 32.64, 26.80, 22.13, 13.50; IR, 1750, 1600, 1470, 1430, 1380, 1330, 1290, 1280, 1230, 1160, 1110, 1100, 1020, 1010, 970, 920, 890, 870, 850, 820, 790, 770, 730; M/e (I%), 140 (3, M+), 122 (1), 111 (55), 98 (10), 84 (100), 83 (30), 57 (35), 55 (65), 41 (65).

15a: ^{1}H NMR, 6.82 (dd, 1H, J=3.6, J=2.5 Hz), 5.59 (dd, 1H, J=3.6, J=2.4 Hz), 3.40-3.10 (m, 1H), 2.00-1.50 (m, 2H), 1.50-1.20 (m, 4H), 1.10-0.80 (m, 3H); ^{13}C NMR, 179.40, 142.65, 110.05, 42.97, 29.96, 28.48, 22.13, 13.48; IR, 1800, 1610, 1560, 1510, 1465, 1380, 1350, 1300, 1280, 1250, 1220, 1200, 1150, 1130, 1110, 1100, 1080, 1020, 980, 970, 950, 910, 890, 850, 740; M/e (I%), 140 (0.7, M+), 125 (1), 112 (25), 98 (55), 84 (55), 83 (55), 70 (60), 55 (50), 41 (100).

16a: ^{1}H NMR, 7.15-7.09 (m, 1H), 4.78 (dd, 2H, J=3.9, J=1.9 Hz), 2.30 (dt, 2H, J=7.0, J=1.7 Hz), 1.70-1.20 (m, 4H), 0.93 (t, 3H, J=7.1 Hz); ^{13}C NMR, 174.68, 144.17, 134.56, 70.00, 29.28, 24.76, 22.01, 13.44; IR, 1775, 1655, 1550, 1465, 1455, 1380, 1350, 1300, 1245, 1200, 1110, 1070, 1040, 1000, 950, 930, 905, 880, 835, 800, 785, 730; M/e (I%), 140 (15, M+), 125 (25), 111 (15), 98 (100), 79 (15), 69 (25), 55 (40), 41 (75).

14b: ^{1}H NMR, 7.48 (dd, 1H, J=5.6, J=1.4 Hz), 6.12 (dd, 1H, J=5.7, J=1.9 Hz), 5.06 (tdd, 1H, J=1.5, J=7.2, J=5.4 Hz), 1.80-1.00 (m, 14H), 1.00-0.50 (t, 3H, J=7.6 Hz); ^{13}C NMR, 173.50, 156.61, 121.50, 83.47, 32.95, 31.57, 29.08(2 C), 28.92, 24.73, 22.37, 13.79; IR, 1750, 1600, 1560, 1465, 1380, 1345, 1285, 1160, 1100, 1075, 1010, 965, 920, 820, 725; M/e (I%), 196 (10, M+), 167 (15), 136 (20), 126 (10), 111 (15), 97 (40), 84 (65), 71 (35), 57 (70), 43 (100), 41 (85).

14c: ^{1}H NMR, 7.63 (dd, 1H, J=5.8, J=1.4 Hz), 6.13 (dd, 1H, J=5.8, J=2.0 Hz), 4.91 (dq, 1H, J=5.8, J=1.7), 2.20-1.90 (m, 1H), 1.01 (d, 3H, J=6.7 Hz), 0.97 (d, 3H, J=6.7 Hz); ^{13}C NMR, 173.20, 155.01, 122.12, 87.86, 31.37, 17.59, 17.23; IR, 1750, 1680, 1600, 1540,1470, 1390, 1370, 1350, 1340, 1330, 1300, 1270, 1240, 1160, 1130, 1100, 1030, 1020, 1000, 960, 950, 910, 890, 850, 830, 810, 790, 740; M/e (I%), 126 (0.5, M+), 111 (0.6), 97 (10), 84 (100), 55 (20), 43 (30), 41 (35).

15c: ^{1}H NMR, 6.84 (dd, 1H, J=3.6, J=2.2 Hz), 5.55 (dd, 1H, J=3.6, J=2.3 Hz), 3.14 (dd, 1H, J=4.7, J=2.4 Hz), 2.40-2.50 (m, 1H), 1.06 (d, 3H, J=6.3 Hz), 0.91 (d, 3H, J=6.8 Hz); ^{13}C NMR, 178.45, 143.09, 107.59, 49.54, 29.54, 20.01, 18.21; IR, 1790, 1620, 1470, 1390, 1370, 1320, 1240, 1150, 1130, 1100, 1080, 1030, 1015, 1000, 950, 870, 730; M/e (I%), 126 (4, M+), 111 (1), 97 (2), 84 (100), 69 (10), 55 (20), 43 (40), 41 (50).

16c: ^{1}H NMR, 7.11 (m, 1H), 4.78 (m, 2H), 2.68 (ds, 1H, J=6.8, J=1.5 Hz), 1.16 (d, 6H, J=6.8 Hz); M/e (I%), 126 (77, M+), 111 (54), 97 (38), 83 (40), 81 (55), 69 (44), 67 (39), 55 (41), 41 (100).

14d: ^{1}H NMR, 7.51 (dd, 1H, J=5.8, J=1.5 Hz), 6.13 (dd, 1H, J=5.8, J=2.0 Hz), 4.87 (dd, 1H, J=3.6, J=1.7 Hz), 2.20-1.50 (m, 5H), 1.50-0.80 (m, 6H); ^{13}C NMR, 173.33, 155.32, 121.74, 87.44, 40.96, 28.24, 27.84, 25.75, 25.46, 25.36; IR, 1750, 1600, 1450, 1410, 1380, 1330, 1290, 1280, 1270, 1260, 1230, 1170, 1150, 1120, 1090, 1080, 1060, 1040, 980, 940, 915, 900, 890, 870, 850, 830, 800, 730; M/e (I%), 166 (10, M+), 137 (20), 124 (20), 111 (35), 97 (20), 91 (30), 84 (100), 83 (40), 55 (85), 41 (45).

16d: ^{1}H NMR, 7.18 (m, 1H), 4.77 (m, 2H), 2.50-2.20 (m, 1H), 2.20-1.50 (m, 4H), 1.50-1.00 (m, 6H); M/e (I%), 166 (10, M+), 121 (10), 93 (5), 84 (100), 83 (45), 67 (25), 55 (90), 41 (60).

14e: p.f. 60-61 °C; ^{1}H NMR, 7.43 (dd, 1H, J=5.8, J=1.5 Hz), 6.05 (dd, 1H, J=5.8, J=2.1 Hz), 4.63 (dd, 1H, J=2.1, J=1.5 Hz), 0.88 (s, 9H); ^{13}C NMR, 173.33, 154.52, 122.38, 90.78, 34.52, 25.40(3C); IR, 1750, 1600, 1475, 1460, 1395, 1365, 1340, 1320, 1300, 1250, 1190, 1160, 1090, 1050, 1030, 1000, 985, 905, 880, 820, 790, 725; M/e (I%), 140 (0.5, M+), 125 (2), 97 (100), 84 (20), 57 (100), 41 (50).

15e: ^{1}H NMR, 6.83 (dd, 1H, J=3.7, J=2.3 Hz), 5.56 (dd, 1H, J=3.7, J=2.4 Hz), 2.93 (t, 1H, J=2.4 Hz), 1.9 (s, 9H); ^{13}C NMR, 142.97, 108.06, 53.41, 29.51, 26.99 (3C); M/e (I%), 140 (40, M+), 125 (30), 111 (10), 97 (50), 95 (30), 84 (10), 81 (20), 79 (40), 69 (20), 67 (30), 53 (30), 41 (100).

Acknowledgment. This work was supported in part by the Ministero della Pubblica Istruzione, Roma.

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19. Compound **16b** was always obtained impure for **14b**; the structure of **16b** was established on the basis of GLC-MS [196 (11, M^+), 111 (95), 98 (100)] and ^1H NMR [7.1 (1H, m), 4.8 (2H, m) ppm] data.

20. No appreciable amount of diphenyl was detected in the sample of PhMgBr used.
21. Compound **14f** showed: 1H NMR, 7.48 (dd, 1H, J=5.7, J=1.5 Hz), 6.15 (dd, 1H, J=5.7, J=2.0 Hz), 6.00-5.50 (m, 1H), 5.30-5.20 (m, 1H), 5.20-5.00 (m, 2H), 2.80-2.40 (m, 2H); ^{13}C NMR, 173.03, 155.81, 131.08, 122.13, 119.65, 82.24, 37.10 ppm.
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