Synthesis of 2-Alkyl-Substituted 1,3-Diketones via the 1,4-Addition of the Grignard Reagents to α,β-Unsaturated Imidates

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4-Propyl-3,5-nonanedione was selectively formed by the reaction of methyl *N*-phenylacrylimidate with ethylmagnesium bromide in 80% yield. Similar diketones were obtained from methyl *N*-phenylcrotonimidate and *N*-phenylcinnamimidate with the Grignard reagents. The coupling of *N*-magnesio α-methoxy enamine and ketenimine, both of which are formed through the initial 1,4-addition of the Grignard reagent to α,β-unsaturated imidate, is the most plausible pathway for the formation of the diketones.

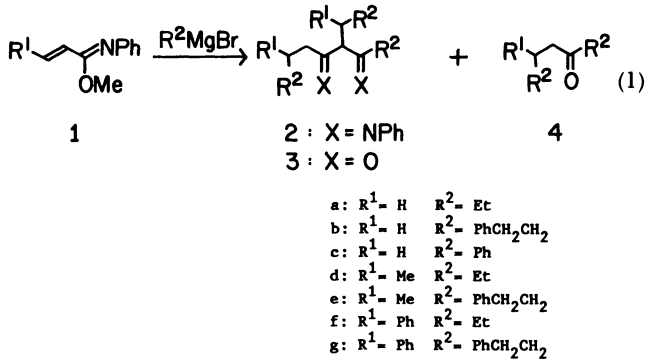
There is presently an interest in imidates (imino ethers) and related compounds from both synthetic and mechanistic points of view.[1] When imidates were treated with acyl halides, imidates gave amides. This reaction has been very important for amide side chain syntheses of β-lactam antibiotics.[2] On the other hand, Meyers et al. reported that the reaction of 2-alkenyldihydro-1,3-oxazines, cyclic version of α,β-unsaturated imidates, with organolithium or the Grignard reagents gave aldehydes or ketones via ketenimines as the key intermediates.[3] It has been reported by Adams and Reifschneider[4] that methyl *N*-phenylsulfonyl-3,3-diphenylpropionimidate is formed by the reaction of methyl *N*-phenylsulfonylcinnamimidate with phenylmagnesium bromide. In this case, however, elimination of methoxymagnesium bromide from the initial 1,4-addition product has not been observed. In this instance we became interested in whether acyclic α,β-unsaturated imidates may afford nucleophilic species upon reaction with organometallic compounds or afford electrophilic species such as ketenimines through further elimination of metal alkoxide. Now we found that the acrylimidates selectively undergo initial 1,4-addition of the Grignard reagents to finally produce 2-alkyl-1,3-diimines as a result of selective coupling between the two intermediates, magnesio enamines and ketenimines.[5] In this paper we wish to report the results in detail and discuss the pathway of the reaction.

Results and Discussion

A series of α,β-unsaturated imidates (**1**) was prepared by the reaction of the corresponding amides and trimethyloxonium tetrafluoroborate according to the literature.[6]

Treatment of methyl *N*-phenylacrylimidate (**1a**) with one equiv. of ethylmagnesium bromide in ether at 0 °C, followed by work-up with dilute hydrochloric acid, afforded 4-propylnonane-3,5-dione (**3a**) as a colorless liquid in 10% yield.

It was then found out that the yield of dione **3a** increased with increase of the amount of ethylmagnesium bromide and the maximum yield (80% yield) was obtained with 6 equiv. of the Grignard reagent (Fig. 1). Ethyl *N*-phenylacrylimidate gave the same diketone (**3a**). Similar treatment of **1a** with 6 equiv. of 2-phenylethylmagnesium and phenylmagnesium bromide also afforded 1,3-diketones **3b** and **3c**, respectively (Table 1, Eq. 1). It was thought that these diketones came out from two moles of **1a** and three moles of the Grignard reagents.



Reaction of crotonimidate (**1b**) and cinnamimidate (**1c**) with the alkyl Grignard reagents afforded 1,3-diimines **2** as stable liquids along with minor amounts of monoketones **4**. The diimines (**2**) could be hydrolyzed with 1 M HCl (1 M=1 mol dm^{-3}) at room tem-

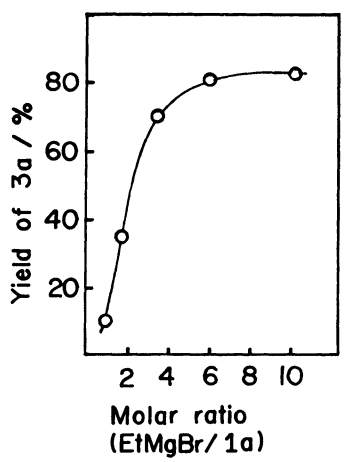
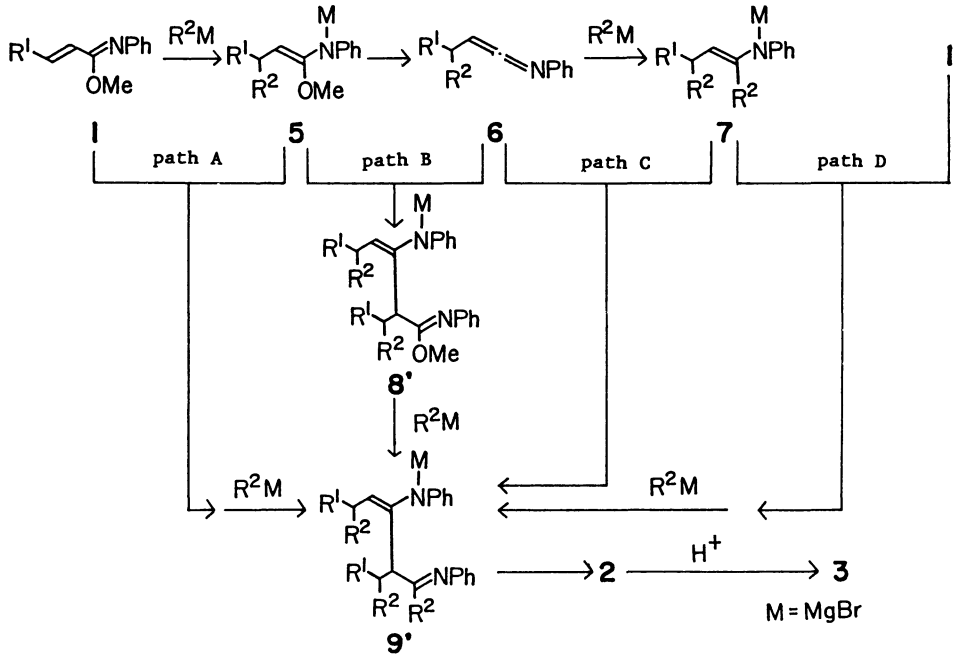


Fig. 1. Effect of the amount of the Grignard reagent.

Table 1. Diimines and Diketones from **1**[a]

1	R^1	R^2	Reaction conditions		Yield/%[b]		
			Temp	Time/h	2	3	4
1a	H	Et	0 °C	7	—	80	—
1a	H	$PhCH_2CH_2$	0 °C	5	—	64	—
1a	H	Ph	0 °C	8	—	74	—
1b	Me	Et	0 °C	4.5	75	80[c]	18
1b	Me	$PhCH_2CH_2$	r.t.	7.5	69	72[c]	21
1c	Ph	Et	0 °C	4	72	85[c]	13
1c	Ph	$PhCH_2CH_2$	r.t.	7.5	26	75[c]	44

a) Reactions were carried out in ether with 6 equiv. of the Grignard reagents. b) Isolated yield. c) The yield of **3** formed by hydrolysis of **2**.

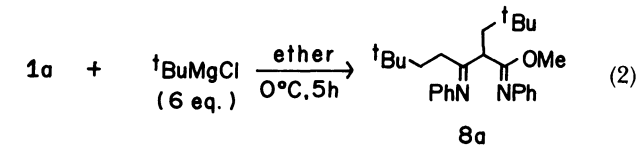


Scheme 1.

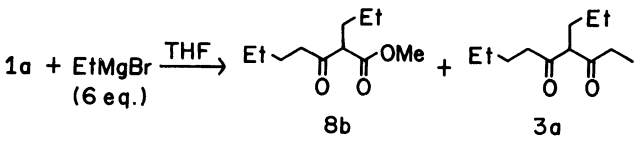
perature for 1—4 days to give 1,3-diketones **3** (Table 1). These results clearly suggest that the reaction of **1a** with the Grignard reagents leads to diimines **2** which are susceptible to hydrolysis during the work-up.

In contract with acryl or β-monosubstituted acrylimidates, α-substituted and β,β-disubstituted imidates, e.g., methacrylimidate, (*E*)-2-methyl-2-butenimidate, and 3-methyl-2-butenimidate gave only monoketones (**4**) upon reaction with alkyl and aryl Grignard reagents.

Several interpretations can be afforded as to the mechanism of formation of diketone **3** (Scheme 1). At first, we tried to detect a presumable key intermediate **6**. But ketenimine **6** was not isolated even by the use of limited quantities of the Grignard reagent or by carring out the reaction at low temperature. When 6 equiv. of *t*-butylmagnesium chloride was used to intercept the reaction at an intermediary stage by preventing further reactions by steric hindrance, β-imino imidate **8a** was obtained in 60% yield (Eq. 2). Moreover, treatment of **1a** with 6 equiv. of ethylmagnesium bromide in tetrahydrofuran (THF), followed by work-up with dilute hydrochloric acid gave 2-valerylpentanoate (**8b**) in 36% yield along with diketone **3a** (29% yield) (Eq. 3). The above results of the formation of β-imino or β-keto esters strongly suggest the presence of **8′** as intermediates in the reaction.

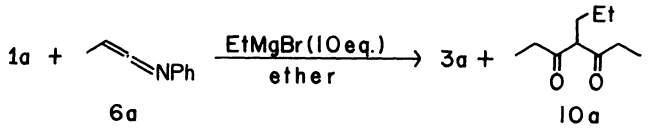


(2)



(3)

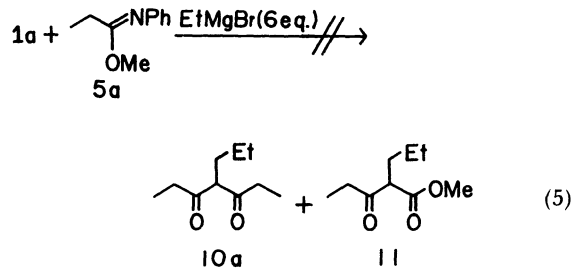
When a mixture of **1a** and 1-phenylimino-1-propene (**6a**), prepared by the reaction of *N*-phenylpropionimidoyl chloride with triethylamine,[7] was treated with 10 equiv. of ethylmagnesium bromide, 4-propyl-3,5-heptanedione (**10a**) was formed in 15% yield as well as **3a** in 43% yield (Eq. 4).



(4)

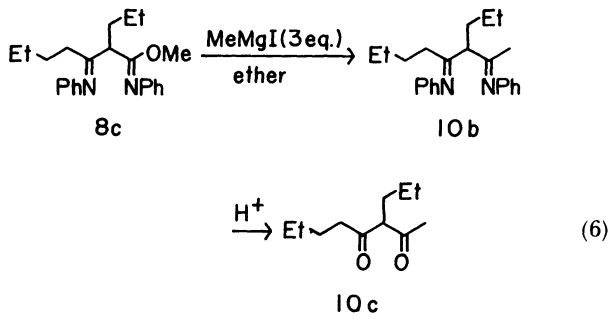
The formation of diketone **10a** suggests that the coupling reaction of *N*-magnesio α-methoxy enamine (**5**) with ketenimine (**6**) is probable (path B). Furthermore, the addition of **1c** to an ethereal solution of the *N*-magnesio enamine, which was in situ prepared from *N*-(1-methylhexylidene)aniline and ethylmagnesium bromide, at 0 °C resulted only in recovering the starting imidate (**1c**) and the imine. These results are not favorable to paths C and D.

In order to test whether the coupling of unsaturated imidate **1** and *N*-magnesio α-methoxy enamine **5** (path A) was possible, the reaction of **1a** with ethylmagnesium bromide was carried out in the presence of methyl *N*-phenylpropionimidate (**5a**). If the coupling reaction between **1** and **5** is possible, *N*-magnesio α-methoxy enamine (**5**) should also react with **5a** to give diketone **10a** and methyl 2-propyl-3-oxopentanoate (**11**) as well as diketone **3a**. The reaction of an equimolar mixture of **1a** and **5a** with 6 molar equiv. of ethylmagnesium bromide in ether at 0 °C for 3 h turned out to give **3a** in 77% yield as a sole product and **5a** was recovered quantitatively (Eq. 5).



(5)

Although the methoxyl group in **5a** was not replaced by the ethyl group upon reaction with ethylmagnesium bromide as shown above, this fact does not deny the path from **8′** to **9′**. A facile replacement of the methoxy group with the Grignard reagent in imidates of the type of **8′** was demonstrated as follows. β-Imino imidate **8c**, the precursor of **8b**, was prepared by the reaction of **1a** and 6 equiv. of ethylmagnesium bromide in THF at 0 °C (vide supra) followed by work-up with aqueous ammonium chloride. When this β-imino imidate **8c** was treated with methylmagnesium iodide in ether at 0 °C, diimine **10b** was formed immediately and, after work-up with dilute hydrochloric acid, diketone **10c** was isolated in 31% yield (Eq. 6). This facilitated alkylation of imidates at the imino nitrogen can be explained by the chelating effect of the imino nitrogen at the β-position toward alkylmagnesium species.



(6)

Finally, the possibility of the initial 1,2-addition, instead of the 1,4-addition discussed so far, of the Grignard reagent to imidate **1** can be deniable by the fact that the reaction of magnesio enamine **7** and **1** did not occur.

By the fact mentioned above, the most plausible pathway seems to involve the initial conjugate addition of the Grignard reagent to imidates affording very reactive *N*-magnesio α-methoxy enamine **5**, which leads to unstable, electrophilic ketenimine **6** upon β-elimination of metal methoxide. The ketenimine (**6**) is selectively alkylated by the strongly nucleophilic species **5** to yield **8′** which are then alkylated at the imidate carbon by the Grignard reagent to give diimine precursor (**9′**). When α-methylated and β,β-dimethylated unsaturated imidates were used, ketenimines **6** could not react with **5** by the steric hindrance, then **6** are attacked by the Grignard reagent to give **7**.

When organolithium reagent was used instead of the Grignard reagents, ketenimine (**6**) was exclusively trapped by the organolithium reagent instead of **5** to give monoketone (**4**).

The most unusual feature of the reaction of α,β-unsaturated imidates with the Grignard reagents is the facile formation of 2-branched 1,3-diketones by the selective coupling of **5** and **6**.

Experimental

General. Boiling points and melting points are uncorrected. IR spectra were measured on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were obtained with a JEOL JNM-C-60M or a JEOL FT-90-Q with tetramethylsilane as an internal standard. Column chromatography was normally effected with Wakogel C-200 (Wako Pure Chemical Industries). GLC analyses were performed on a Shimadzu GC-7A chromatograph using a column packed with Silicone OV-17 (3 mm×3 m). Trimethyloxonium tetrafluoroborate[9] and α,β-unsaturated imidate[6] were prepared according to the literature. The structure of the known compounds were

established on the basis of their spectroscopic properties and from descriptions in the literature.

Reaction of Methyl *N*-Phenylacrylimidate (1a) with Grignard Reagents. To a stirred ether solution of the Grignard reagent (18.6 mmol), **1a** (0.50 g, 3.1 mmol) was added at 0 °C and stirred for 5—8 h at 0 °C. Then the solution was poured into 1 M HCl at 0 °C and stirred for 1 h. The resulting mixture was extracted with ether and the organic layer was washed with $NaHCO_3$ aq. then brine and dried over $MgSO_4$. After filtration, the solvent was removed and the residue was purified by column chromatography (silica gel-hexane/chloroform) to give diketone.

4-Propyl-3,5-nonanedione (3a): bp 129—130 °C/11 mmHg (1 mmHg=133.322 Pa.); IR (neat) 2970, 1730, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.91 (6H, m), 1.04 (3H, t, J=7 Hz), 1.27 (4H, m), 1.53 (2H, m), 1.82 (2H, m), 2.46 (2H, t, J=7 Hz), 2.49 (2H, q, J=7 Hz), and 3.67 (1H, t, J=7 Hz); MS m/z 198 (M^+).

Found: C, 72.70; H, 11.43%. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18%.

1,9-Diphenyl-4-(3-phenylpropyl)-3,5-nonanedione (3b): IR (neat) 3060, 2860, 1725, 1695, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=1.50 (8H, m), 2.60 (10H, m), 3.42 (1H, t, J=7 Hz), and 7.12 (15H, s).

Found: C, 84.51; H, 8.13%. Calcd for $C_{30}H_{34}O_2$: C, 84.46; H, 8.03%.

1,5-Diphenyl-2-benzyl-1,3-pentanedione (3c): mp 66—67 °C (MeOH); IR (KBr) 1710, 1680, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.79 (4H, bs), 3.30 (2H, d, J=7 Hz), 4.79 (1H, t, J=7 Hz), 7.23 (10H, s), and 7.70 (5H, m); MS m/z 342 (M^+).

Found: C, 83.96; H, 6.46%. Calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48%.

Reaction of Methyl *N*-Phenylcrotonimidate (1b), Methyl *N*-Phenylcinnamimidate (1c) with Alkyl Grignard Reagents. To a stirred ether solution of Grignard reagent (18.6 mmol), imidate (3.1 mmol) was added at 0 °C. After further stirring at 0 °C or r.t., the resulting mixture was poured into aqueous ammonium chloride then extracted with ether and dried over $MgSO_4$. After filtration, the solvent was removed and distilled with Glass Tube Oven to give monoketone. The resulting residue was purified by column chromatography (silica gel-hexane/chloroform) to give diimine. To a solution of diimine (1 mmol) in ether (10 ml), 1 M HCl (40 ml) was added and stirred for 1—4 days. The resulting mixture was extracted with ether and washed with brine, dried over $MgSO_4$. After filtration, the solvent was removed and the residue was purified by column chromatograpy (silica gel-hexane/chloroform) to give diketone. The following compounds were prepared.

5-Methyl-3-heptanone (4d): bp 152—154 °C (lit,[10] 153—155 °C).

***N,N'*-Diphenyl-7-methyl-4-(1-methylpropyl)-3,5-nonanediimine (2d):** IR (neat) 2960, 1640, 1595, 755, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (15H, m), 2.20 (10H, m), 3.73 (1H, d, J=7 Hz), and 6.87 (10H, m).

Found: C, 82.71; H, 9.64; N, 7.60%. Calcd for $C_{26}H_{36}N_2$: C, 82.93; H, 9.64; N, 7.44%.

7-Methyl-4-(1-methylpropyl)-3,5-nonanedione (3d): bp 133—134 °C/17 mmHg; IR (neat) 2960, 1720, and 1695 cm^{-1}; ^1H NMR (CCl_4) δ=0.89 (19H, m), 2.10 (8H, m), and 3.34 (1H, d, J=7 Hz); MS m/z 226 (M^+).

Found: C, 74.50; H, 11.57%. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58%.

5-Methyl-1,7-diphenyl-3-heptanone (4e): bp 174—175 °C/0.30 mmHg; IR (neat) 3030, 2930, 1715, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=1.10 (3H, d, J=7 Hz), 2.10 (10H, m), 3.37 (1H, m), and 7.12 (10H, s).

Found: C, 85.65; H, 8.61%. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63%.

***N,N'*-Diphenyl-7-methyl-4-(1-methyl-3-phenylpropyl)-1,9-diphenyl-3,5-nonanediimine (2e):** IR (neat) 3030, 2930, 1640, 1595, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=0.97 (6H, m), 2.10 (16H, m), 3.50 (1H, d, J=7 Hz), and 6.89 (25H, m).

Found: C, 87.66; H, 8.25; N, 4.33%. Calcd for $C_{44}H_{48}N_2$: C, 87.37; H, 8.00; N, 4.63%.

7-Methyl-4-(1-methyl-3-phenylpropyl)-1,9-diphenyl-3,5-nonanedione (3e): IR (neat) 3030, 2930, 1690, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=0.80 (3H, d, J=7 Hz), 0.83 (3H, d, J=7 Hz), 2.00 (16H, m), 3.32 (1H, d, J=7 Hz), and 7.05 (15H, s).

Found: C, 84.75; H, 8.35%. Calcd for $C_{32}H_{38}O_2$: C, 84.45; H, 8.42%.

5-Phenyl-3-heptanone (4f): bp 120—125 °C/2.5 mmHg (lit,[11] 255 °C).

***N,N'*-Diphenyl-4-(1-phenylpropyl)-7-phenyl-3,5-nonanediimine (2f):** IR (neat) 3030, 2930, 1640, 1595, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=1.54 (19H, m), 3.48 (1H, d, J=7 Hz), and 6.90 (20H, m).

Found: C, 86.62; H, 8.00; N, 5.20%. Calcd for $C_{36}H_{40}N_2$: C, 86.35; H, 8.05; N, 5.59%.

4-(1-Phenylpropyl)-7-phenyl-3,5-nonanedione (3f): IR (neat) 3040, 2970, 1720, 1700, 760, and 705 cm^{-1}; ^1H NMR (CCl_4) δ=0.68 (9H, m), 1.67 (8H, m), 3.17 (2H, m), 3.93 (1H, d, J=7 Hz), and 7.15 (10H, s); MS m/z 350 (M^+).

Found: C, 82.51; H, 8.74%. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63%.

1,5,7-Triphenyl-3-heptanone (4g): bp 194—196 °C/0.19 mmHg; IR (neat) 3030, 2915, 1715, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=2.10 (11H, m), 7.12 (15H, s).

Found: C, 87.97; H, 7.37%. Calcd for $C_{25}H_{26}O$: C, 87.68; H, 7.65%.

***N,N'*-Diphenyl-1,7,9-triphenyl-4-(1,3-diphenylpropyl)-3,5-nonanediimine (2g):** IR (neat) 3030, 2930, 1640, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=2.08 (16H, m), 3.50 (1H, d, J=7 Hz), and 6.89 (35H, m).

Found: C, 89.26; H, 6.91; N, 3.54%. Calcd for $C_{54}H_{52}N_2$: C, 88.97; H, 7.19; N, 3.84%.

1,7,9-Triphenyl-4-(1,3-diphenylpropyl)-3,5-nonanedione (3g): IR (neat) 3040, 2970, 1720, 1700, 760, and 705 cm^{-1}; ^1H NMR (CCl_4) δ=1.60 (6H, m), 1.76 (10H, m), 3.95 (1H, d, J=7 Hz), and 7.15 (25H, s).

Found: C, 87.41; H, 7.35%. Calcd for $C_{42}H_{42}O_2$: C, 87.16; H, 7.31%.

Reaction of 1a with *t*-Butylmagnesium Chloride. To a stirred ether solution of *t*-butylmagnesium chloride (31 mmol), ether solution of **1a** (0.50 g, 3.1 mmol) was added at 0 °C and stirred at r.t. for 5 h. After usual work-up, the residue was purified by column chromatography (alumina-dichloromethane) to give methyl *N*-phenyl-2-(2,2-dimethylpropyl)-6,6-dimethyl-3-phenyliminoheptanimidate (**8a**) (0.38 g, 60%); bp 165—170 °C/0.80 mmHg; IR (neat) 3030, 2960, 1660, 1245, 750, and 700 cm^{-1}; ^1H NMR (CCl_4) δ=0.77 (18H, m), 1.90 (6H, m), 3.67 (1H, t, J=7 Hz), 3.80 (3H, s), and 6.95 (10H, m); MS m/z 406 (M^+). Found: C, 79.74; H, 9.71; N,

6.58%. Calcd for $C_{27}H_{38}N_2O$: C, 79.76; H, 9.42; N, 6.89%.

Reaction of 1a with Ethylmagnesium Bromide in THF. According to the general procedure, 0.50 g (3.1 mmol) of **1a** and ethylmagnesium bromide (31 mmol) were treated in THF. After usual work-up, the residue was purified by column chromatography (silica gel–hexane/ethyl acetate) to give **3a** (111 mg, 36%), methyl 2-valerylpentanoate (**8b**) (89 mg, 29%); bp 130—135 °C/20 mmHg; IR (neat) 2960, 1740, and 1235 cm^{-1}; ^1H NMR (CCl_4) δ=0.95 (6H, m), 1.83 (10H, m), 3.29 (1H, t, J=7 Hz), and 3.67 (3H, s); MS m/z 200 (M^+).

Reaction of 1a and *N*-(1-Propenylidene)aniline (6a) with Ethylmagnesium Bromide. According to the general procedure, **1a** 0.50 g (3.1 mmol) and **6a** 0.40 g (3.1 mmol) were treated with 31 mmol of ethylmagnesium bromide in ether at 0 °C. After usual work-up, the residue was purified by column chromatography (silica gel–hexane/chloroform) to give **3a** (132 mg, 43%), 4-propyl-3,5-heptanedione (**10a**) (40 mg, 15%); IR (neat) 2950, 1720, 1695, and 1460 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (3H, t, J=7 Hz), 0.99 (6H, t, J=7 Hz), 1.45 (4H, m), 2.38 (4H, q, J=7 Hz), and 3.49 (1H, t, J=7 Hz); MS m/z 170 (M^+).

Reaction of Methyl *N*-Phenyl-3-(phenylimino)-2-propylheptanimidate (8c) with Methylmagnesium Iodide. 1a (0.50 g, 3.1 mmol) and 10 equiv. of ethylmagnesium bromide were treated in THF at 0 °C, then poured into aqueous ammonium chloride, and extracted with ether, the organic layer was dried ($MgSO_4$) and concentrated. The crude mixture was dissolved in ether (5 ml), added to methylmagnesium iodide in ether at 0 °C and stirred for 5 min then poured into 1 N HCl, stirred for 1 h. After usual work-up and distillation (125—130 °C/10 mmHg) to give a mixture of **3a** and 3-propyl-2,4-octanedione (**10c**); MS m/z 184 (M^+), which was separated by GLC.

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