A New Convenient Synthesis of 4-Substituted 4-Methyl-2-pentanones

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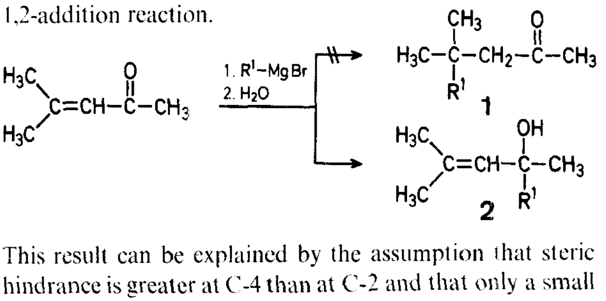
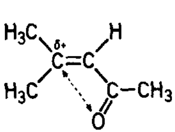
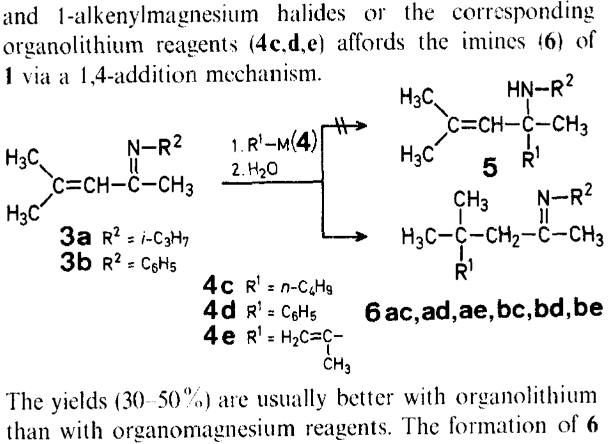
4-Substituted 4-methyl-2-pentanones (**1**) cannot be obtained by reaction of a Grignard reagent with mesityl oxide: with saturated[1], phenylic[2], vinylic[3], and allylic[4] organomagnesium compounds, only the alcohols **2** are obtained via a 1,2-addition reaction.



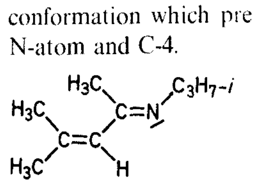
This result can be explained by the assumption that steric hindrance is greater at C-4 than at C-2 and that only a small positive charge δ+ is located at C-4: in fact, the preferred conformation of mesityl oxide is *s-cis*, slightly twisted[5], which leads to a decrease of the positive charge at C-4.



We report here that the reaction of *N*-isopropyl- and *N*-phenylimines (**3a**,**b**) of mesityl oxide with alkyl-, phenyl-, and 1-alkenylmagnesium halides or the corresponding organolithium reagents (**4c**,**d**,**e**) affords the imines (**6**) of **1** via a 1,4-addition mechanism.



The yields (30–50%) are usually better with organolithium than with organomagnesium reagents. The formation of **6** instead of **5** may, in turn, be explained by a greater steric hindrance at C-2 than at C-4 and by a preferred *s-trans* conformation which prevents any interaction between the N-atom and C-4.

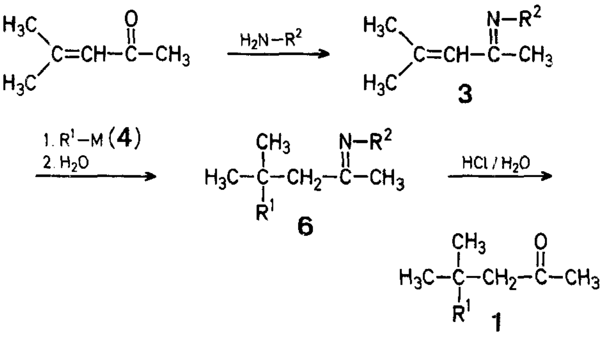


In fact, we observed a linear dependence of the ¹H-N.M.R. shift of the $(CH_3)_2C=$ and $HC=$ groups on the (increasing) amount of added $Eu(FOD)_3$. The variation is greater for the $HC=$ group than for the $(CH_3)_2C=$ group: $\Delta(\delta_{CH=})/\Delta(\delta_{(CH_3)_2C=}) = 0.53/0.15$; these results are in agreement with the *s-trans* conformation. Reverse results were obtained for mesityl oxide: $\Delta(\delta_{CH=})/\Delta(\delta_{(CH_3)_2C=}) = 2.0/3.32$; this is in agreement with the well-established *s-cis* conformation.

It is thus once more shown that in the reaction of saturated or vinylic organometallic compounds with α,β-unsaturated imines 1,4-addition takes place much easier than with α,β-unsaturated carbonyl compounds[6,7].

On the other hand, allylic organometallic compounds ($H_2C=CH-CH_2-M$, M = ZnBr, MgBr, Li) react with the ketimines **3a**,**b** via a 1,2-addition mechanism to give amines **5** as reported for α,β-unsaturated aldimines[7] and for most of the α,β-unsaturated carbonyl compounds investigated[8].

The acidic hydrolysis[9,10] of ketimines **6** affords the corresponding ketones (**1**) in good yields (80–90%). Thus, 4-substituted 2-pentanones (**1**) can be conveniently prepared from mesityl oxide.



The organometallic reagents were prepared by known methods: butyl- and phenylmagnesium bromide in ether, butyllithium[11] and phenyllithium[12] in ether, 2-propenylmagnesium bromide[13] in tetrahydrofuran, and 2-propenyllithium[14] in ether. The I.R. spectra were recorded on a Beckman IR 4240 spectrometer. The N.M.R. spectra were recorded on a Perkin-Elmer 24 A spectrometer using TMS as internal standard.

N-Isopropyl-4-methyl-3-penten-2-imine (3a):

This compound is prepared from *N*-isopropyl-2-propanimine (99.2 g, 1 mol) according to Ref.[15,16]; yield: 64 g (46%); b.p. 58°/24 torr.

$C_9H_{17}N$	calc.	C 77.69	H 12.23
(139.2)	found	77.54	11.98

I.R. (neat): $\nu_{max} = 3080, 1640, 830$ (CH=C); 1660 cm⁻¹ (C=N).

¹H-N.M.R. (CCl_4): δ = 0.80–1.20 (m, 6H, 2CH₃); 1.50–2.20 (m, 9H, 3H₃C—C=); 3.25–3.80 [m, 1H, CH(CH₃)₂]; 5.40–5.65 ppm (m, 1H, C=CH).

¹H-N.M.R. [CCl_4/0.25 molar $Eu(FOD)_3$]: δ = 1.0–1.50 (m, 6H, 2CH₃); 1.80–2.20 [m, 6H, (CH₃)₂C=]; 2.60 (s, 3H, H₃C—C=N); 3.50–4.20 [m, 1H, CH(CH₃)₂]; 5.95–6.20 ppm (m, 1H, C=CH).

4-Methyl-*N*-phenyl-3-penten-2-imine (3b):

This compound is prepared from mesityl oxide (304.3 g, 3.1 mol) and aniline (93.13 g, 1 mol) in benzene according to Ref.[17]; yield: 86 g (50%); b.p. 125°/15 torr.

$C_{12}H_{15}N$	calc.	C 83.24	H 8.67
(173.3)	found	82.84	8.91

I.R. (neat): $\nu_{max} = 3090, 1640, 830$ (CH=C); 1655 (C=N); 1595, 1495, 760, 700 cm⁻¹ (C₆H₅).

¹H-N.M.R. (CCl_4): δ = 1.35–2.35 (m, 9H, 3CH₃); 5.45–5.90 (m, 1H, CH=); 6.25–7.35 ppm (m, 5H, C₆H₅).

Reaction of α,β-Unsaturated Ketimines (3a,b) with Organometallic Compounds (4); General Procedure:

The ketimine (**3a**,**b**; 0.1 mol) is dissolved in ether or tetrahydrofuran (30 ml). This solution is slowly added (1 h) at room temperature to a stirred solution of the organometallic compound (0.2 mol) prepared in the usual manner: the temperature increases slightly (5 or 10°). The resultant mixture is stirred overnight at room temperature and is then hydrolysed by the addition of a saturated

Table. *N*-4-Disubstituted 4-Methyl-2-pentanimines (**6**) prepared from Ketimines (**3**) and Organometallic Compounds (**4**)

6	R^1	R^2	Yield [%]	b.p./torr	Other physical data	Molecular formula[a]	I.R. (neat) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
ac	n-C_4H_9	i-C_3H_7	25	85°/12		$C_{13}H_{27}N$ (195.4)	1650 (C=N)	0.90–1.50 [m, 21 H, 5 CH_3, $-(CH_2)_3$]; 1.65 (s, 3 H, $H_3C-C=$); 2.20–2.45 (m, 2 H, $-CH_2-C=$); 3.30–3.75 [m, 1 H C<u>H</u>$(CH_3)_2$]
bc	n-C_4H_9	C_6H_5	30	155°/16	n_D^{20}: 1.5125	$C_{16}H_{25}N$ (231.4)	1650 (C=N); 1595, 1495, 760, 700 (C_6H_5)	0.75–1.10 (m, 9 H, 3 CH_3); 1.10–1.50 [m, 6 H, $-(CH_2)_3-$]; 1.62 (s, 3 H, $H_3C-C=$); 2.22 (s, 2 H, $-CH_2-C=$); 6.35–7.30 (m, 5 H, C_6H_5)
ad	C_6H_5	i-C_3H_7	48	132–133°/11	n_D^{20}: 1.5030 d_4^{20}: 0.916	$C_{15}H_{23}N$ (217.3)	1650 (C=N); 1600, 1500, 765, 705 (C_6H_5)	0.90–1.50 (m, 12 H, 4 CH_3); 1.70 (s, 3 H, $H_3C-C=$); 2.45–2.70 (m, 2 H, CH_2); 3.20–3.70 [m, 1 H, C<u>H</u>$(CH_3)_2$]; 7.00–7.55 (m, 5 H, C_6H_5)
bd	C_6H_5	C_6H_5	50	200°/16	n_D^{20}: 1.5677 d_4^{20}: 1.002	$C_{18}H_{21}N$ (251.4)	1650 (C=N); 1595, 1495, 760, 700 (C_6H_5)	1.15–1.45 (m, 9 H, 3 CH_3); 2.50 (s, 2 H, CH_2); 6.15–7.45 (m, 10 H, 2 C_6H_5)
ae	$H_2C=C(CH_3)-$	i-C_3H_7	30	74°/11		$C_{12}H_{23}N$ (181.3)	3100, 895 ($H_2C=C$); 1655 (C=N)	0.95–1.35 (m, 12 H, 4 CH_3); 1.55–2.10 (m, 6 H, 2 $H_3C-C=$); 2.20–2.50 (m, 2 H, CH_2); 3.30–3.75 [m, 1 H, C<u>H</u>$(CH_3)_2$]; 4.60–5.00 (m, 2 H, $H_2C=C$)
be	$H_2C=C(CH_3)-$	C_6H_5	47	152°/14	n_D^{20}: 1.5280 d_4^{20}: 0.935	$C_{15}H_{21}N$ (215.3)	1650 (C=N); 3100, 890 ($H_2C=C$); 1600, 1595, 760, 700 (C_6H_5)	1.05–1.30 (m, 6 H, 2 CH_3); 1.50–1.95 (m, 6 H, 2 $H_3C-C=$); 2.40 (s, 2 H, CH_2); 4.60–4.85 (m, 2 H, $H_2C=C$); 6.15–7.35 (m, 5 H, C_6H_5)

[a] The microanalyses showed the following maximum deviation from the calculated values: C, ±0.32; H, ±0.20.

aqueous solution (~150 ml) of ammonium chloride. The aqueous layer is extracted with ether (3 × 100 ml). The organic layer is washed with water (with 20% sodium hydroxide solution in the case of phenylic organometallic compounds), and dried with potassium carbonate. The solvent is removed under reduced pressure and the ketimine isolated by distillation under reduced pressure.

Hydrolysis of the Ketimines 6 to the 4-Substituted 4-Methyl-2-pentanones 1; General Procedure:

To a stirred solution of the ketimine **6** (0.05 mol) in ether (30 ml), 4 normal hydrochloric acid (25 ml, 0.1 mol) is gradually added. Stirring is continued for 4 h at 30°. The organic layer is then separated and the aqueous layer is extracted with ether (3 × 50 ml). The organic phases are combined, washed with water, and dried with potassium carbonate. The solvent is removed under reduced pressure and the ketone isolated by distillation under reduced pressure.

4,4-Dimethyl-2-octanone (**1c**); yield (from **6bc**): 7.0 g (90%); b.p. 81°/19 torr; n_D^{20}: 1.4321 (Ref.[18], b.p. 62–64°/7 torr; n_D^{20}: 1.4250).

I.R. (neat): $\nu_{max} = 1720\ cm^{-1}$ (C=O).

^{1}H-N.M.R. (CCl_4): $\delta = 0.70$–1.05 (m, 9H, 3CH_3); 1.05–1.50 [m, 6H, $(CH_2)_3$]; 1.95 (s, 3H, H_3C-CO); 2.15 ppm (s, 2H, CH_2).

4-Methyl-4-phenyl-2-pentanone (**1d**); yield (from **6ad**): 7.5 g (85%); b.p. 128°/15 torr; n_D^{20}: 1.5118 (Ref.[19], b.p. 134°/22 torr).

I.R. (neat): $\nu_{max} = 1720$–1705 (C=O); 1602, 1498, 765, 700 cm^{-1} (C_6H_5).

^{1}H-N.M.R. (CCl_4): $\delta = 1.30$ (s, 6H, 3CH_3); 1.60 (s, 3H, H_3C-CO); 2.55 (s, 2H, CH_2); 6.95–7.45 ppm (m, 5H, C_6H_5).

5-Oxo-2,3,3-trimethyl-2-hexene (**1e**); yield (from **6be**): 5.6 g (80%); b.p. 60°/15 torr; n_D^{20}: 1.4450.

$C_9H_{16}O$	calc.	C 77.14	H 11.43
(140.2)	found	77.29	11.35

I.R. (neat): $\nu_{max} = 1720$–1710 (C=O); 3090, 1638, 892 cm^{-1} ($H_2C=$).

^{1}H-N.M.R. (CCl_4): $\delta = 1.05$ (s, 6H, CH_3); 1.67 (s, 3H, $H_3C-C=$); 1.95 (s, 3H, H_3C-CO); 2.40 (s, 2H, CH_2-CO); 4.65–4.80 ppm (m, 2H, $H_2C=$).

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