Hyperbasic Media: Metalation of Ketimines; a Fast Convenient Synthesis of 1,4-Diketones

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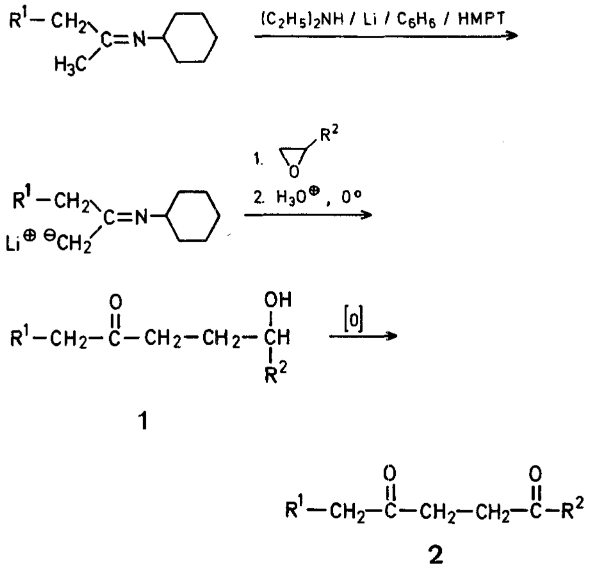
Regiospecific alkylation of ketones presents a considerable problem in organic synthesis. Generally, the simple reaction of electrophiles with enolates gives rise to mixtures of several compounds[1]. We have previously shown that the reaction of lithium salts of carbanions having the negative charge in a position α to an imine function proceed regioselectively. For instance, alkylation of an imine derived from a methyl ketone results in the alkylation on the methyl group only[2].

These anions are generated from imines by treatment with very powerful bases: "activated dialkylamides" in hexamethylphosphoric triamide; but it is sometimes possible to use more classical bases such as lithium diisopropylamide in ether. Lithiated imines are very useful intermediates in organic synthesis and we reported recently that reaction with 2,3-dichloropropene, followed by hydrolysis with concentrated sulfuric acid, provided 1,4-diketones $R-CO-CH_2-CH_2-COCH_3$[2].

We wish to report now a convenient and general preparation of these compounds which involves condensation with an oxirane. The reaction gives the ketols **1** which are oxidised by the Jones reagent in high yields to give the 1,4-diketones **2**.

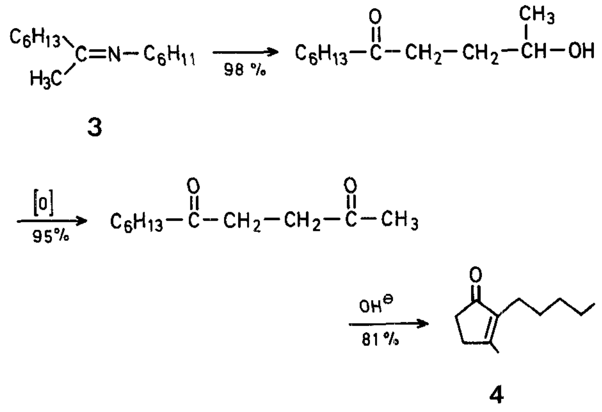


This condensation of epoxides with lithiated imines is a highly efficient procedure and gives good yields (Tables 1 and 2). Reaction is possible even with not very reactive compounds such as cyclohexene oxide.

However, these ketols are easily dehydrated and it is sometimes necessary to oxidise the crude product directly (For instance, the ketol derived from ring opening of styrene oxide cannot be distilled).

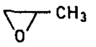
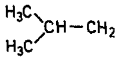
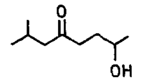
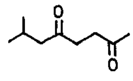
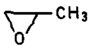
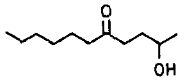
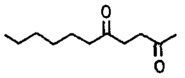
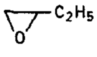
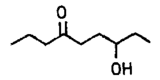
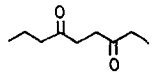
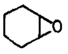
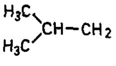
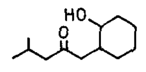
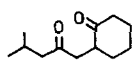
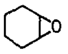
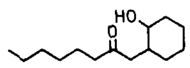
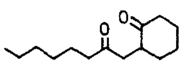
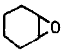
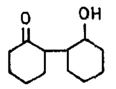
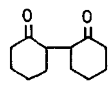
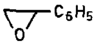
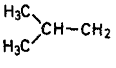
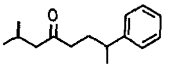
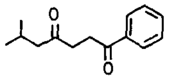
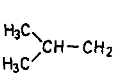
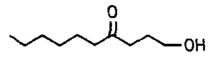
This attractive synthetic route permits ready access to 1,4-diketones and is interesting because the ketimines are easily available from ketones.

Synthesis of dihydrojasmone (**4**) is a good example of this method: it was obtained in pure form in 75% overall yield from imine **3**.



Moreover, we succeeded in obtaining 1,4-diketones in a one flask procedure by using 2 mol of the imine. The anionic site α to the imine function reacted with iodine. There is

Table 1. Reaction of Oxiranes with Lithiated Imines $LiCH_2-C(R)=N-C_6H_{11}$-c

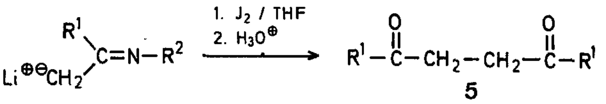
	Oxirane	R in Imine	Ketol (**1**)	Yield (%)[a]	1,4-Diketone (**2**)	Yield (%)[a]
a		 $(H_3C)_2CH-CH_2$		90		92
b		n-C_6H_{13}		98		95
c		n-C_3H_7		95		95
d		 $(H_3C)_2CH-CH_2$		62		90
e		n-C_6H_{13}		91		89
f		$-(CH_2)_4-$		65		90
g		 $(H_3C)_2CH-CH_2$		[b]		[b]
h		 $(H_3C)_2CH-CH_2$		75	—	
i		n-C_6H_{13}		81	—	

[a] Yield of distilled recrystallised product.

[b] The crude product was oxidised; 45% overall yield.

probably formation of an α iodo-imine (it is the same for the anionic site α to esters[3]) and this reacts then with the excess anion.

A summary of 1,4-diketones obtained from this coupling reaction is shown in Table 3.



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In short, it can be said that lithiated ketimines provide a rapid synthetic route to a wide variety of symmetric or unsymmetric 1,4-diketones.

Metalation and Condensation of Imines:

A mixture of diethylamine (4.05 g, 0.055 mol), hexamethylphosphoric triamide (12 ml), anhydrous benzene (11 ml) and hammer-wrought lithium (0.39 g, 0.055 g.-atom) was stirred under argon until the metal was completely dissolved.

The temperature was held at 20° and dry tetrahydrofuran (15 ml) was added to the dark red solution. Then the amide was cooled to −30° and the imine (0.05 mol) in tetrahydrofuran (15 ml) was slowly added. After being allowed to stand for one hour at −5°, the oxirane (0.055 mol) was added drop-wise at −15° (0° if it is not very reactive).

The solution was discoloured and was allowed to stir for four hours at room temperature. It was extracted with ether and the solvents were then removed.

In order to eliminate hexamethylphosphoric triamide completely, it was necessary to wash the residue with 2 *N* hydrochloric acid (30 ml) and to extract it again with pentane. The organic layer was washed with water and aqueous sodium carbonate; after drying with magnesium sulfate, the solvent was removed again and the residue distilled. The ketols are summarised in Table 2.

Oxidation of Ketoalcohol:

A solution of sodium dichromate (1.2 g, 0.04 mol), water (5 ml), and concentrated sulfuric acid (0.013 mol) is added over 40 min to a stirred mixture of the ketoalcohol (0.01 mol) and water (2 ml).

The temperature rises to 60° during the addition and the solution becomes black. The mixture is cooled, extracted with ether, washed twice with water, dried over magnesium sulfate, and distilled or recrystallized. The diketones thus prepared are summarised in Table 2.

Table 2. Physical Data for Ketols (**1a–i**) and Diketones (**2a–g**) shown in Table 1

Product	M.p. or B.p.	n_D^{20}	I.R. (neat) ν_{max} cm^{-1}	^{1}H-N.M.R. (CCl_4) δ ppm	Elemental Analysis			
1a	80°/0.1 torr	1.4460	1710, 3400	1.10 (d, 3H), 2.4 (m, 4H), 3.65 (m, 1H)	$C_9H_{18}O_2$ (158)	calc. found	C 68.35 68.78	H 11.39 11.24
2a	51°/0.1 torr	1.4350	1710	2.11 (s, 3H), 2.25 (t, 2H), 2.55 (s, 4H)	$C_9H_{16}O_2$ (156)	calc. found	C 69.23 69.24	H 10.25 10.60
1b	95°/0.05 torr	—	1700, 3350	2.37 (t, 2H), 2.48 (d, 2H), 3.65 (m, 1H)	$C_{11}H_{22}O_2$ (186)	calc. found	C 70.9 71.6	H 11.9 12.1
2b	70–73°/0.001 torr m.p. 40°	—	1715	0.9 (t, 3 H), 2.11 (s, 3H), 2.57 (s, 4H)	—			
1c	70°/0.1 torr	1.4480	1710, 3400	0.85 (t, 6H) 2.50 (m, 4H), 3.50 (m, 1H)	$C_9H_{18}O_2$ (158)	calc. found	C 68.35 68.42	H 11.39 11.35
2c	55°/0.1 torr	1.4360	1710	1.5 (m, 2H), 2.35 (t, 2H), 2.43 (q, 2H), 2.55 (s, 4H)	$C_9H_{16}O_2$ (156)	calc. found	C 69.23 68.96	H 10.25 10.59
1d	m.p. 54°	—	1710, 3350	0.88 (d, 6H), 2.96 (m, 2H)	$C_{12}H_{22}O_2$ (198)	calc. found	C 72.68 72.43	H 11.18 H 10.81
2d	84°/0.3 torr	1.4640	1708	0.89 (d, 6H), 2.74 (m, 1H)	$C_{12}H_{20}O_2$ (196)	calc. found	C 73.43 73.16	H 10.27 10.33
1e	120°/0.1 torr	1.4810	1705, 3370	—	$C_{14}H_{26}O_2$ (226)	calc. found	C 74.33 74.32	H 11.50 11.48
2e	56°/0.05 torr	1.4650	1710	—	$C_{14}H_{24}O_2$ (224)	calc. found	C 75.00 74.69	H 10.71 10.74
1f	110°/0.1 torr	1.5035	1700, 3400	—	$C_{12}H_{20}O_2$ (196)	calc. found	C 73.43 73.68	H 10.27 10.47
2f	m.p. 71°	—	1685	—	$C_{12}H_{18}O_2$ (194)	calc. found	C 74.22 73.89	H 9.28 9.44
2g	125°/0.07 torr	1.5170	1710, 1685, 750, 690	0.87 (d, 6H), 2.68 (t, 2H), 3.11 (s, 2H)	$C_{14}H_{18}O_2$ (218)	calc. found	C 77.06 76.69	H 8.25 8.51
1h	65°/0.1 torr	—	1710, 3400	1.75 (m, 3H), 2.35 (m, 4H), 3.50 (t, 2H)	$C_8H_{16}O_2$ (144)	calc. found	C 66.66 66.31	H 11.11 H 11.24
1i	105°/0.1 torr	1.4550[a]	1705, 3390	2.40 (m, 4H), 3.50 (t, 2H)	$C_{10}H_{20}O_2$ (172)	calc. found	C 69.76 70.16	H 11.62 11.86

[a] n_D^{23} given.

Table 3. Synthesis and Physical Data for Diketones (**5**) R—CO—CH_2CH_2—CO—R

	R	Yield (%)[a]	B.p. or m.p.	I.R. (neat) ν_{max} cm^{-1}	^{1}H-N.M.R. (CCl_4) δ ppm	Elemental Analysis			
a	C_2H_5	80	68°/0.1 torr m.p. 35°	1700	2.55 (s, 4H)	$C_8H_{14}O_2$ (142)	calc. found	C 67.60 67.26	H 9.86 10.02
b	n-C_3H_7	81	m.p. 25°	1700	2.55 (s, 4H)	$C_{10}H_{18}O_2$ (170)	calc. found	C 70.58 69.90	H 10.58 10.64
c	i-C_4H_9[b]	84	90°/0.1 torr	1700	2.55 (s, 4H)	$C_{12}H_{22}O_2$ (198)	calc. found	C 72.72 72.39	H 11.11 11.25
d	n-C_6H_{13}	91	m.p. 68.5°	1690	2.55 (s, 4H)	$C_{16}H_{30}O_2$ (254)	calc. found	C 75.59 75.46	H 11.81 11.11

[a] Yields of distilled or recrystallised products.

[b] $n_D^{20} = 1.4370$.

Coupling of Ketimines:

Under an argon atmosphere, butyllithium (0.08 mol) was slowly added to a stirred solution of diisopropylamine (8.1 g, 0.08 mol) in tetrahydrofuran (10 ml) at −10°. The temperature was then held at +15° for 20 minutes.

The imine (0.08 mol) in tetrahydrofuran (20 ml) was slowly added to the amide at −20°. After being allowed to stand for 1 hour at −5°; the solution was slowly added to iodine (10.1 g, 0.04 mol) dissolved in tetrahydrofuran (30 ml) at −70°. In 1 hour the temperature raises to +15°, then 3 *N* hydrochloric acid (80 ml) was added at −20° and the mixture stirred for 6 hours at room temperature. The solution was extracted with ether, the organic layer washed with sodium thiosulfate, water, dried on magnesium sulfate, and concentrated in vacuum. The diketone was isolated by distillation. The physical data of the diketones are summarised in Table 3.

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