A Mild and Convenient Synthesis of 3-Methylene-2-pyrrolidinones

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The α-methylene-carbonyl unit is found in a number of natural products having biological activities[1]. Although various methods for the construction of α-methylene-γ-butyrolactones have been developed[2,3,4], only a few examples are reported for the preparation of their nitrogen analogues, 3-methylene-2-pyrrolidinones.

The introduction of an α-methylene unit in the 2-pyrrolidinone ring is a widely used method which provides moderate to good yields of the product[5–8]. The recently developed method for palladium-catalyzed carbonylation of vinyl iodides is of interest in view of synthetic chemistry; however this approach gave a moderate yield of a mixture of regioisomers[9].

We have recently described a new dianion **2**[10] derived from 2-methylpropenamide **1** which is a highly effective reagent for the synthesis of α-methylene-γ-butyrolactones from carbonyl compounds[11,12].

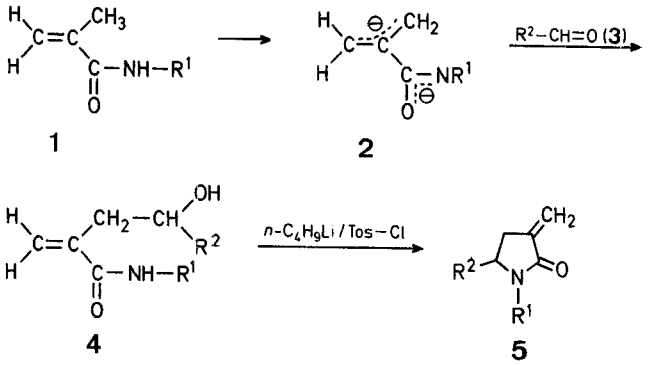
We now report that amide alcohols **4**, prepared from the dianion **2** and an aldehyde **3**[10], can serve as efficient intermediates for a one-pot synthesis of 3-methylene-2-pyrrolidinones **5** under very mild conditions. Thus, treatment of the amide alcohols **4**, with 2 equivalents of *n*-butyllithium at −78°C followed by addition of *p*-toluenesulfonyl chloride gave 3-methylene-2-pyrrolidinones **5** in good yields after chromatography on silica gel (Table).

This procedure makes available of a wide variety of the 5-alkyl-3-methylene-2-pyrrolidinones **5** by using the readily

Table. 3-Methylene-2-pyrrolidinones **5** prepared

Product	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
5a	94	oil[c]	$C_{19}H_{19}NO$ (277.4)	1670, 1640, 920, 760, 700[d]	1.12, 1.74 (2d, J = 7.2 Hz, 3H); 2.39–3.36 (m, 2H); 4.20–4.38, 4.56–4.72 (2m, 1H); 4.88, 5.62 (2q, J = 7.2 Hz, 1H); 5.24–5.44 (m, 1H); 6.02–6.25 (m, 1H); 6.88–7.52 (m, 10H)
5b	78	65–75°	$C_{19}H_{25}NO$ (283.4)	1660, 1640, 910, 700	0.44–1.96 (m, 11H); 1.69 (dd, J = 7.2, 2.4 Hz, 3H); 2.34–2.72 (m, 2H); 3.11–3.29, 3.60–3.84 (2m, 1H); 5.26 (t, J = 2.7 Hz, 1H); 5.36 (q, J = 7.2 Hz, 1H); 5.97 (t, J = 2.7 Hz, 1H); 7.22–7.60 (m, 5H)
5c	65	oil[c]	$C_{21}H_{31}NO$ (313.5)	1670, 1645, 910, 700[d]	0.77–1.44 (m, 17H); 1.69 (dd, J = 7.2, 2.4 Hz, 3H); 2.23–3.03 (m, 2H); 3.18–3.43, 3.58–3.87 (2m, 1H); 5.31 (s, 1H); 5.44 (q, J = 7.2 Hz, 1H); 6.02 (s, 1H); 7.22–7.56 (m, 5H)
5d	42	151–151.5°	$C_{17}H_{15}NO$ (249.3)	1670, 1640, 930, 750, 700	2.59–2.85, 3.22–3.59 (2m, 2H); 5.27 (dd, J = 8.4, 3.0 Hz, 1H); 5.46 (t, J = 2.7 Hz, 1H); 6.23 (t, J = 2.7 Hz, 1H); 7.00–7.67 (m, 10H)
5e	67	87–89.5°	$C_{15}H_{25}NO$ (235.4)	1660, 1635, 915	0.55–1.98 (m, 11H); 1.45 (s, 9H); 2.48–2.64 (m, 2H); 3.62–3.76 (m, 1H); 5.12 (s, 1H); 5.78 (s, 1H)
5f	60	119–120°	$C_{15}H_{19}NO$ (229.3)	1660, 1640, 920, 700	1.31 (s, 9H); 2.32, 2.48 (2s, 1H); 2.92–3.27 (m, 1H); 4.82 (d, J = 7.5 Hz, 1H); 5.18 (s, 1H); 5.97 (s, 1H); 7.06–7.42 (m, 5H)
5g	96	85–86°	$C_{17}H_{27}NO$ (261.4)	1680, 1655, 935	0.55–2.12 (m, 21H); 2.47–2.72 (m, 2H); 3.42–3.80 (m, 2H); 5.16 (t, J = 2.7 Hz, 1H); 5.83 (t, J = 2.7 Hz, 1H)
5h	75	99–100°	$C_{17}H_{21}NO$ (255.4)	1680, 1655, 940, 720	0.68–1.98 (m, 10H); 2.40–2.72 (m, 1H); 2.99–3.37 (m, 1H); 3.58–3.98 (m, 1H); 4.65 (dd, J = 8.4, 2.4 Hz, 1H); 5.26 (t, J = 2.7 Hz, 1H); 6.01 (t, J = 2.7 Hz, 1H); 7.10–7.45 (m, 5H)
5i	80	oil[c]	$C_{19}H_{33}NO$ (291.5)	1690, 1660, 925[d]	0.62–2.04 (m, 27H); 2.24–2.97 (m, 2H); 3.44–3.94 (m, 2H); 5.22 (s, 1H); 5.90 (s, 1H)

[a] Yields of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.38, H ±0.15, N ±0.28.
[c] These oily products were unstable and polymerized on distillation.
[d] I.R. spectra recorded as film.



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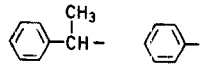
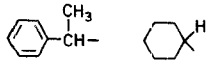
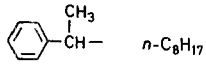
4,5	R^1	R^2	4,5	R^1	R^2
a			e	t-C_4H_9	
b			f	t-C_4H_9	
c		n-C_8H_{17}	g		
d			h		
			i		n-C_8H_{17}

available *N*-substituted-2-methylpropenamides **1** and appropriate aldehydes **3** as starting materials. The use of methanesulfonyl chloride in place of *p*-toluenesulfonyl chloride led to a substantial reduction in the yield[13].

1-(α-Methylbenzyl)-3-methylene-5-phenyl-2-pyrrolidinone (5a); Typical Procedure:

To a solution of *N*-(α-methylbenzyl)-2-(β-hydroxyphenethyl)-propenamide (**4a**; 0.89 g, 3.0 mmol) in dry tetrahydrofuran (20 ml) at −78 °C is added a 1.70 molar solution of *n*-butyllithium in hexane (3.6 ml, 6.1 mmol) under an argon atmosphere. After stirring for 30 min, a solution of *p*-toluenesulfonyl chloride (0.57 g, 3.0 mmol) in dry tetrahydrofuran (5 ml) is added. The mixture is stirred for 30 min and allowed to warm to room temperature during 18 h. The reaction is quenched with saturated ammonium chloride (10 ml) and the mixture is poured into ether (30 ml). The layers are separated, the aqueous phase is extracted with ether (3 × 30 ml), and the combined organic fractions are washed with brine (2 × 50 ml). The ether layer is dried with sodium sulfate, filtered, and the solvent is removed in vacuum. The crude product obtained is purified by column chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent to afford pure **5a**; yield: 0.78 g (94%).

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