1,4-Addition of *N,N*-Disubstituted Phenylacetamides to 2-Arylmethylene-1,4-butanolides†

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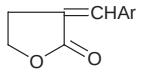
The 1,4-addition reaction of lithium derivatives of *N,N*-disubstituted phenylacetamides with 2-arylmethylene-1,4-butanolides gives the corresponding *N,N*-disubstituted 2-(1-aryl-2-carbamoyl-2-phenylethyl)-1,4-butanolides **3a–f** as diastereoisomeric mixtures with 40–68% yields.

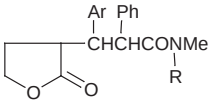
The reactivity of unsaturated small ring lactones as acceptors in Michael reactions has not received as much attention as that of their acyclic analogues, esters of 2,3-unsaturated carboxylic acids.[1] We focused our interest on 2-arylmethylene-1,4-butanolides because they can be used successfully as building blocks for the synthesis of a large variety of natural products containing a γ-lactone ring, many of which have pharmacological activity.[2,3]

In 1986 it was reported by Murray *et al.*[4] that reaction of $LiCH_2CN$ with 2-arylmethylene-1,4-butanolides occurs *via* 1,2-addition to give the corresponding 2-cyanomethylene-3-methylenetetrahydrofurans. The same regioselectivity was observed also for the addition of Reformatsky reagents.[5]



1a Ar = Ph
b Ar = C_6H_4OMe-*p*
c Ar = C_6H_4Cl-*p*
d Ar = H

2a R = Ph
b R = Me



3a R = Ph Ar = Ph
b R = Me Ar = Ph
c R = Ph Ar = C_6H_4OMe-*p*
d R = Me Ar = C_6H_4OMe-*p*
e R = Me Ar = C_6H_4Cl-*p*
f R = Ph Ar = H

In the course of our studies on the Michael reaction we found that the reaction of a lithiated *N*-methyl-*N*-phenylamide derivative of phenylacetic acid **2a** (LDA, THF, 0 °C) with 2-phenylmethylene-1,4-butanolide **1a** at 0 °C occurs *via* 1,4-addition. Examination of the IR and ^{1}H NMR spectra as well as the analytical data of the obtained crystalline compound **3a** (50% yield) revealed that it is one of the possible four diastereoisomers. The ^{1}H NMR spectrum of the crude reaction mixture showed singlets for the *N*-methyl protons of all diastereoisomers but using column chromatography we could isolate, besides the main isomer, only two other isomers in small quantities. The structure of these isomers was confirmed by their IR and ^{1}H NMR spectra.

Our efforts to increase the yield changing the reaction conditions led to a maximum yield of 55% of **3a** (25 °C, 5 h). Refluxing of the reaction mixture or extension of the reaction time up to 24 h gave only 15–16% of the expected product. The use of another deprotonating reagent ($LiNH_2$ in liquid ammonia or $TiCl_4/Et_3N$ in THF) as well as performing the reaction under PTC-conditions (50% NaOH, DMSO, TEBA) failed to give the expected product.

We continued our study on the behaviour of the 2-arylmethylene-γ-lactones using the above optimal conditions with the *N,N*-dimethylamide derivative of phenylacetic acid **2b**. Also, besides 2-phenylmethylene-1,4-butanolide **1a** the 4-methoxyphenyl (**1b**) and 4-chlorophenyl (**1c**) were used as Michael acceptors, as well as the commercially available α-methylene-γ-butyrolactone (**1d**).

We found that for all 2-arylmethylene-1,4-butanolides the expected products of conjugate addition were obtained in yields of between 40 and 68% as mixtures of diastereoisomers. In each case the predominant isomer in the reaction mixture was purified by recrystallisation while generally the other isomers were isolated in small amounts by column chromatography.

We then investigated the behaviour of 2-methylene-1,4-butanolide **1d** under the same reaction conditions with the *N*-methyl-*N*-phenylamide derivative of phenylacetic acid (**2a**). The expected product of conjugate addition (**3f**) as obtained as an oil in 45% yield. The two possible diastereoisomers were separated by column chromatography and identified.

The observed regioselectivity of the studied reaction can not be explained in terms of electronic or substituent effects. The only possible explanation is on the basis of the HSAB-hypothesis. Hard ambident nucleophiles such as $LiCH_2CN$[4] or the Reformatsky reagent, prepared from 2-bromoacetate,[5] react with the hard reaction centre of the unsaturated system, the carbonyl group. By contrast, the soft ambident nucleophiles, obtained from the amides of the phenylacetic acid, attack the soft centre of the Michael acceptor and the reaction is a typical 1,4-addition.

The observed regioselectivity of the studied reaction indicates a high probability to prepare new γ-lactones with functionalized lateral chains.

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Experimental

Mps were determined with a microscope containing a 'Boetius' type hot-stage (Germany) and are uncorrected. IR spectra were obtained on a Specord 71 IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM 250 spectrometer (250 MHz) using $SiMe_4$ as internal reference. The starting phenylacetamides[6] and 2-arylmethylene-1,4-butanolides[7] were prepared according to literature procedures.

General Procedure for the Synthesis of 2-*Substituted Lactones* **3a–f**.—To a solution of LDA (2.2 mmol) in THF (2 ml) at 0 °C was added dropwise the corresponding phenylacetamide **2** (2 mmol) in THF (3 ml). The reaction mixture was stirred for 15 min and then the lactone **1** (2 mmol) in THF (4–8 ml) was added and the temperature was allowed to raise to ambient. The mixture was stirred for 5 h, quenched with 2 ml 2 M HCl and THF was evaporated *in vacuo*. Then 20 ml water was added and after cooling the residue formed was filtered off and purified by recrystallisation or column chromatography on Merck silica gel 60 (0.063–0.200 mm).

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Physical and Spectroscopic Data for the Predominant Diastereoisomers of **3a**–**f**.—**3a**: yield 55%, mp 211–213 °C (ethanol); IR (Nujol ν_{max}/cm^{-1} 1765 (CO_2) 1655 (CON); δ_H($CDCl_3$, 250 MHz) 1.97–2.10 (m, 1H), 2.16–2.30 (m, 1H), 3.01–3.09 (m, 1H), 3.25 (s, 3H, NCH_3), 3.98–4.19 (m, 4H, H), 6.76–7.39 (m, 15 H, H_{arom}) (Found: C, 77.94; H, 6.50; N, 3.40. $C_{26}H_{25}NO_3$ requires C, 78.17, H, 6.31, N, 3.51%). **3b**: yield 68%, mp 216–218 °C (ethanol); IR (Nujol) ν_{max}/cm^{-1} 1745 (CO_2), 1635 (CON); δ_H($CDCl_3$, 250 MHz) 2.11–2.33 (m, 2H), 2.92 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 3.03–3.13 (m, 1H), 4.03 (dd, 1H, PhC*H*CHPhCON, *J* 9.9, 6.6 Hz), 4.11–4.33 (m, 2H), 4.48 (d, 1H, PhC*H*CON, *J* 9.9 Hz), 6.99–7.11 (m, 10 H, H_{arom}) (Found: C, 74.63; H, 6.97; N, 3.92. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.87; N, 4.15%). **3c**: yield 40%; IR (Nujol) ν_{max}/cm^{-1} 1775 (CO_2), 1655 (CON); δ_H($CDCl_3$, 250 MHz) 2.00–2.05 (m, 1H), 2.20–2.24 (m, 1H), 2.99–3.06 (m, 1H), 3.25 (s, 3H, NCH_3), 3.63 (m, 3H, OCH_3), 3.95–4.15 (m, 4H, H), 6.51–6.55 (m, 2H, H_{arom}, 6.75–6.81 (m, 4H, H_{arom}), 6.97–7.01 (m, 5H, H_{arom}), 7.26–7.40 (m, 3H, H_{arom}) (Found: C, 75.62, H, 6.52, N, 3.17. $C_{27}H_{27}NO_4$ requires C, 75.50, H, 6.34, N, 3.26%). **3d**: yield 48%; IR (Nujol) ν_{max}/cm^{-1} 1765 (CO_2), 1635 (CON); δ_H ($CDCl_3$, 250 MHz) 2.11–2.25 (m, 2H), 2.92 (s, 3H, NCH_3), 2.97–3.07 (m, 1H), 3.00 (s, 3H, NCH_3), 3.68 (s, 3H, OCH_3), 4.00 (dd, 1H, PhC*H*CHPhCON, *J* 9.7, 6.5 Hz)), 4.10–4.30 (m, 2H), 4.45 (d, 1H, PhC*H*CON, *J* 9.8 Hz), 6.60–6.64 (m, 2H, H_{arom}), 6.91–6.95 (m, 2H, H_{arom}), 7.04–7.10 (m, 5H, H_{arom}) (Found: C, 71.91, H, 6.56, N, 3.90. $C_{22}H_{25}NO_4$ requires C, 71.91, H, 6.86, N, 3.81%). **3e**: yield 59%; IR (Nujol) ν_{max}/cm^{-1} 1770 (CO_2), 1635 (CON); δ_H($CDCl_3$, 250 MHz) 1.75–1.83 (m, 1H), 2.26–2.40 (m, 1H), 2.97 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.34 (td, 1H, PhC*H*CON, *J* 9.1, 4.5 Hz), 3.63–3.77 (m, 2H), 4.05 (dd, 1H, *J* 16.7, 7.9 Hz), 5.08 (d, 1H, *J* 11.4 Hz), 6.93–7.32 (m, 9H, H_{arom}) (Found: C, 67.57, H, 6.04, N, 3.74. $C_{21}H_{22}ClNO_3$ requires C, 67.83, H, 5.96, N, 3.77%). **3f**: yield 45%, oil; IR (neat) ν_{max}/cm^{-1} 1765 (CO_2), 1650 (CON); δ_H($CDCl_3$, 250 MHz), 1.74–2.02 (m, 2H), 2.21–2.38 (m, 2H), 2.45–2.55 (m, 1H), 3.25 (s, 3H, NCH_3), 3.99 (dd, 1H, *J* 9.4, 5.8 Hz), 4.07–4.17 (m, 1H), 4.22–4.30 (m, 1H), 6.93–7.34 (m, 10H, H_{arom}) (Found: C, 74.16, H, 6.85, N, 4.00. $C_{20}H_{21}NO_3$ requires C, 74.28, H, 6.55, N, 4.33%).

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