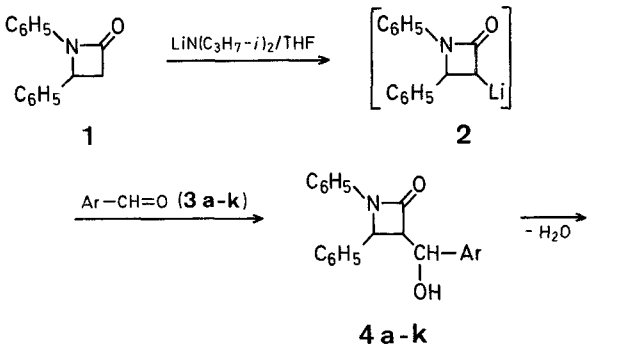

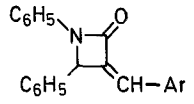

A Simple Preparation of 3-Benzylidene-2-azetidinones

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Because of its presence in β-lactam antibiotics, the 2-azetidinone system has been the subject of intensive study[1]; in addition it is a useful, reactive synthon[2]. Interest in 3- and 4-substituted 2-azetidinones is increasing[3]. Fletcher and Kay[4] prepared 3-methylene-2-azetidinones starting with dibromoalkanecarboxamides, while Shibuya and coworkers[5] described a synthesis of 3-alkylidene-2-azetidinones via the 3-trimethylsilyl derivative prepared from the 2-azetidinone. We have now developed a useful and simple method for preparing the 3-arylidene derivatives **5**.

Although the reactivity of the protons in position 3 of 1,4-diphenyl-2-azetidinone (**1**) seems to be rather low, it is possible to abstract one proton by action of a strong base under aprotic conditions. While some such reagents cause opening of the β-lactam ring[6], this does not occur with lithium diisopropylamide in tetrahydrofuran. Thus, the non-isolable intermediate **2** was generated, immediate quenching of which with an appropriate aromatic aldehyde **3a-k** gives rise to the hydroxy compounds **4** as isolable, stable crystalline compounds (see Table 1). Dehydration of **4** should then give the desired compounds **5**. Although many procedures have been described for the dehydration of similar compounds[7] most of these failed when applied to **4**[6]. Only the reaction with *p*-tosyl chloride in anhydrous pyridine gave satisfactory results. In the cases of **4a** and **4g**, only the use of trifluoromethanesulfonyl chloride was successful, and in the case of **4f** the reaction with acetic anhydride yielded **5f** in good yield. These results seem to show the expected dependence of reactivity on the substituent of the aromatic aldehyde. The data for the compounds **5** prepared are summarized in Table 2.

Table 1. 3-Arylhydroxymethyl-1,4-diphenyl-2-azetidinones **4a-k**

Product	Ar	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	I.R. (KBr) [cm^{-1}] ν_{OH}	I.R. (KBr) [cm^{-1}] $\nu_{C=O}$	^{1}H-N.M.R. ($CDCl_3$)[c] δ [ppm]
4a	C_6H_5	25	157–158 (CH_3OH)	$C_{22}H_{19}NO_2$ (329.4)	3450	1725	2.93 (bs, 1H); 3.42 (m, 1H); 5.18 (d, 1H); 5.38 (d, 1H)
4b	*p*-Cl–C_6H_4	65	158–160 (CH_3OH)	$C_{22}H_{18}ClNO_2$ (363.8)	3425	1715	3.40 (bs, 1H); 3.35 (m, 1H); 5.10 (d, 1H); 5.28 (d, 1H)
4c	*p*-O_2N–C_6H_4	90	170–172 (CH_3OH)	$C_{22}H_{18}N_2O_4$ (374.4)	3380	1720	3.40 (bs, 1H); 3.42 (m, 1H); 5.12 (d, 1H); 5.48 (d, 1H)
4d	*p*-Br–C_6H_4	68	172–174 (CH_3OH)	$C_{22}H_{18}BrNO_2$ (408.3)	3430	1715	3.50 (m, 1H); 3.36 (m, 1H); 5.13 (d, 1H); 5.33 (d, 1H)
4e	*p*-HO–C_6H_4	32	176–178 (CCl_4)	$C_{22}H_{19}NO_3$ (345.4)	3430	1735	2.92 (bs, 1H); 3.38 (m, 1H); 4.89 (d, 1H); 5.20 (d, 1H)
4f	*p*-$(H_3C)_2N$–C_6H_4	70	178–180 (CH_3OH)	$C_{24}H_{24}N_2O_2$ (372.4)	3445	1735	2.40 (d, 1H); 3.40 (m, 1H); 5.15 (m, 2H)
4g	*p*-H_3C–C_6H_4	62	178–180 (xylene)	$C_{23}H_{21}NO_2$ (343.4)	3480	1730	2.29 (d, 1H); 3.37 (m, 1H); 5.15 (d, 1H); 5.30 (d, 1H)
4h	*o*-O_2N–C_6H_4	80	192–194 (CH_3OH)	$C_{22}H_{18}N_2O_4$ (374.4)	3330	1720	6.10 (d, 1H); 3.5 (m, 1H); 5.26 (d, 1H); 5.92 (d, 1H)[d]
4i	*m*-O_2N–C_6H_4	57	172–174 (CH_3OH)	$C_{22}H_{18}N_2O_4$ (374.4)	3340	1725	6.14 (d, 1H); 3.5 (q, 1H); 5.15 (d, 1H); 5.35 (d, 1H)[d]
4k	*o*-Cl–C_6H_4	86	171–173 (CH_3OH)	$C_{22}H_{18}ClNO_2$ (363.8)	3340	1715	3.35 (bs, 1H); 3.61 (m, 1H); 5.15 (d, 1H); 5.73 (d, 1H)

[a] Yield, based on **1** of isomer mixture.
[b] The microanalyses and mass spectra were in satisfactory agreement with the expected results (C ±0.36, H ±0.08, N ±0.15).
[c] Data for H_{arom} not given.
[d] In DMSO-d_6 solution.

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Table 2. 3-Arylidene-1,4-diphenyl-2-azetidinones **5a-k**

Product[a]	Yield[b] [%]	Boiling time [h]	m.p. [°C][c] (solvent)	Molecular formula[d]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (solvent)[e] δ [ppm]	
5a	30	—[f]	334–335 (CH_3CN)	$C_{22}H_{17}NO$ (311.4)	1715	($CDCl_3$)	6.28 (1 H); 5.40 (1 H)
5b	20	20	225–227 (CCl_4)	$C_{22}H_{16}ClNO$ (345.8)	1725	($CDCl_3$)	6.23 (1 H); 5.38 (1 H)
5c	50	6	166–168 (CH_3OH)	$C_{22}H_{16}N_2O_3$ (356.4)	1720	($CDCl_3$)	6.31 (1 H); 5.42 (1 H)
5d	50	5	250–251 (acetone)	$C_{22}H_{16}BrNO$ (390.3)	1715	($CDCl_3/CF_3COOH$)	6.42 (1 H); 5.56 (1 H)
5e	15	8	142–144 (CH_3OH)	$C_{22}H_{17}NO_2$ (327.4)	1720	($CDCl_3$)	6.15 (1 H); 5.30 (1 H)
5f	70	—[f]	212–213 (acetone	$C_{24}H_{22}N_2O$ (354.5)	1715	($CDCl_3$)	6.17 (1 H); 5.30 (1 H)
5g	25	—[f]	254–255 (acetone)	$C_{23}H_{19}NO$ (325.4)	1715	($CDCl_3/CF_3COOH$)	6.38 (1 H); 5.46 (1 H)
5h	60	18	149–150 (CH_3OH)	$C_{22}H_{16}N_2O_3$ (356.4)	1720	($CDCl_3$/DMSO-d_6)	6.84 (1 H); 5.54 (1 H)
5i	50	8	156–158 (CH_3OH)	$C_{22}H_{16}N_2O_3$ (356.4)	1725	($CDCl_3$)	6.35 (1 H); 5.45 (1 H)
5k	20	18	188–190 (CH_3OH/ acetone)	$C_{22}H_{16}ClNO$ (345.8)	1715	($CDCl_3$/DMSO-d_6)	6.76 (1 H); 5.48 (1 H)

[a] For Ar, see Table 1.
[b] Yield based on **4**.
[c] Not corrected.
[d] The microanalyses were in satisfactory agreement with the calculated values (C ±0.16, H ±0.04, N ±0.13).
[e] Signals for H_{arom} and substituents in Ar not listed.
[f] See experimental.

3-Arylhydroxymethyl-1,4-diphenyl-2-azetidinones 4; General Procedure:
Reactions are carried out under a nitrogen atmosphere. Tetrahydrofuran is dried over molecular sieve 4 Å before use. To a solution of lithium diisopropylamide, prepared from diisopropylamine (0.02 mol) and *n*-butyllithium (0.02 mol; 15% suspension in hexane) in dry tetrahydrofuran (10 ml) is added a solution of 1,4-diphenyl-2-azetidinone (**1**; 0.01 mol) in tetrahydrofuran (100 ml) at −78 °C. After 5 min a solution of the aromatic aldehyde **3** (0.015 mol) in tetrahydrofuran (50 ml) is added to the reaction mixture at the same temperature. After being stirred at −78 °C for 30 min, the mixture is poured into water (200 ml) saturated with sodium chloride, the organic layer is separated, dried with anhydrous sodium sulfate, and evaporated (Table 1).

3-Benzylidene-1,4-diphenyl-2-azetidinones 5; General Procedure:
A solution of **4** (0.01 mol) and tosyl chloride (0.02 mol) in dry pyridine (50 ml) is boiled under reflux (time, see Table 2). After cooling, ice/water (50 ml) is added, and the mixture is twice extracted with chloroform. The combined extracts are twice washed with dilute hydrochloric acide and once with water, dried with sodium sulfate, and evaporated. The residue, product **5**, is recrystallized. For preparation of **5a** or **5g**, a solution of **4a** or **4g** (0.01 mol) and trifluoromethanesulfonyl chloride (0.01 mol) in dry pyridine (30 ml) is boiled for 8 or 7 h. Product **5f** may be prepared by boiling of **4f** (0.01 mol) in acetic acid (100 ml) for 5 min, subsequent cooling yields **5f** as yellow crystals.

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