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On the Azetidin-2-one Ring Formation. A ^{1}H NMR Investigation.

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Abstract. Azetidin-2-ones were prepared by addition of phenylacetic acid chloride to substituted benzal-anilines in DMF. The effect of temperature and substituents at the benzal-anilines on the reaction mechanism was investigated, carrying out the reaction in DMF d_7 in an NMR probe of a Bruker 400-MHz spectrometer, at 25 and 60 °C. Proton signals, arising from two kinds of intermediates, a 2-phenyl-N-(α-chlorobenzyl)-acetanilide (**6**) and a nitrogen-charged adduct (**7**), suggest that two competitive mechanisms play a role in the formation of trans and cis azetidin-2-ones.

One of the most employed synthetic routes to azetidin-2-ones is the reaction between an acid halide and an imine, in the presence of an amine base (Staudinger reaction[1]). Two general mechanistic pathways have been hypothesized[2,3]. The first path **K** involves the reaction of a ketene, preformed or formed *in situ*, with an imine to yield a zwitterionic intermediate which undergoes a conrotatory [2+2] cycloaddition reaction[4].

The second pathway **I** starts with the acylation of the imine by the acid halide giving a N-acyliminium halide[5]. This intermediate species can undergo two possible pathways.

Proton abstraction would produce the same zwitterionic intermediate reported in the ketene-imine reaction and could then close to form the β-lactam in a [2+2] conrotatory cycloaddition reaction.

Alternatively, a halide could add to the N-acyliminium ion to form an α-halideamide[6,7,8]. Proton abstraction would then produce a stabilized carbanion that could directly form the β-lactam by a halogen displacement reaction. Generally, it is difficult to predict the stereochemical outcome of Staudinger reaction, because the reported results greatly depend on the reaction conditions employed, on steric factors and on substituent effects. The stereochemistry of the resultant β-lactams is also affected by the order of addition[9] of the base and by the substitution pattern of the acid

halide.

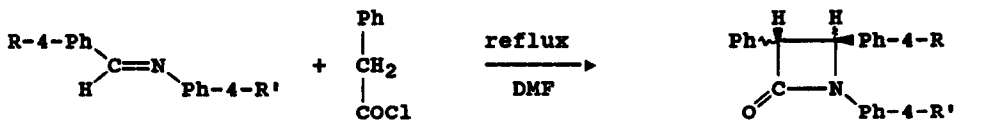
In fact, it was reported that α-electron-donating substituents on acid halides are possibly able to stabilize a transition state, producing cis stereochemistry[10] of the β-lactams.

In order to obtain further mechanistic information concerning Staudinger reaction, benzal-anilines (1) and phenylacetic acid chloride (2) in DMF were used as starting materials. This acid chloride was selected because the α-phenyl-group does not possess a pair of free electrons; no amine base was added to our reaction mixture to avoid the possible formation of a ketene and to push the reaction through the second reported pathway I.

Results

The reaction between substituted benzal-anilines 1 and phenylacetic acid chloride 2 in DMF, at reflux temperature, afforded only trans azetidin-2-ones (3) (Procedure A).

Scheme 1



1 2 3=trans β-lactam

	R	R'
a	Cl	Br
b	CH_3	CH_3
c	H	H
d	CH_3	H
e	OCH_3	Cl

	R	R'
f	F	H
g	Cl	H
h	Br	H
i	NO_2	H
l	OCH_3	H

The ^1H NMR spectra of the azetidinones 3 showed the doublets of two hydrogens on the azetidinonic ring, between δ 5 and 4, with a coupling constant J=2.5 Hz indicating trans stereochemistry at the β-lactam ring system. On the contrary, by treating 1 and 2, at 25 °C (Procedure A'), cis (3') and trans (3) isomers were recovered from the reaction mixture.

Only selected benzalanilines 1 (a, b, c, d, e) and the corresponding β-lactams 3 and 3' were reported in the Experimental. The ^1H NMR spectra of more soluble cis azetidinones 3' showed the aromatic signals at a higher field than the trans isomers, and the two azetidinonic doublets, between δ 5.5 and 5.0, with a coupling constant J=6.2 Hz.

Figure 1 shows a perspective view of the trans 1-(4'-chlorophenyl)-4-(4'-methoxyphenyl)-3-phenyl-azetidin-2-one (**3e**). The conjugation between the chlorophenyl ring and the N-C-O group is well evident from the values of the bond lengths N-C(2) and N-C(5) (1.367(2) and 1.404(2) Å) arising from X-Ray analysis.

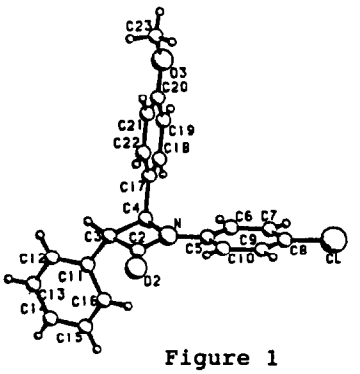


Figure 1

The yields of these reactions, depending on different substituted-benzalanilines, are reported in Table 1 at 25°C and at reflux temperature. When R is an electron-donating group the reaction yields are higher, indicating an inductive effect of these substituents on the azomethinic bond. No cis azetidinone was recovered from the reaction mixture at reflux-temperature.

Table 1. Reaction between Equimolecular Amounts of Benzal-anilines and Phenylacetic Acid Chloride in DMF, at Reflux and at 25 °C for 24 h: Azetidinone Yields (%).

	R	R'	T_R-Yield trans	T_{25}-Yield trans+cis	trans/cis ratio
3a	Cl	Br	36.5	35.2	60/40
3b	CH_3	CH_3	31.7	32.1	90/10
3c	H	H	45.5	44.9	80/20
3d	CH_3	H	48.3	47.2	95/5
3e	OCH_3	Cl	73.1	72.8	80/20
3f	F	H	27.7		
3g	Cl	H	42.5		
3h	Br	H	46.5		
3i	NO_2	H	38.8		
3l	OCH_3	H	46.4		

To investigate the stereoselectivity and substituent effects, and to obtain further information about the reacting species, this cyclization was carried out in a Bruker 400 MHz NMR probe at 25 and 60 °C, in DMF d_7. The benzal-anilines **1a** and **1b**, substituted with electron-

withdrawing and electron-donating groups, respectively, were selected to get the most intelligible systems for the ^1H NMR analysis.

The ^1H NMR spectra of a mixture containing **1a** and **2** at 25 °C were recorded every ten minutes. After twenty minutes, the spectrum showed, together with the decreasing signals of the starting materials, the following increasing signals: two singlets at δ 7.98 (1H) and 7.35 (5H), two couples of doublets at 7.65 (2H) and 7.26 (2H) and at 7.12 (2H) and 7.26 (2H), a singlet at 3.76 (2H). These signals account for the formation of the 2-phenyl-N-(α-chloro-p-chlorobenzyl)-p-bromoacetanilide (**6a**) (Scheme 2) and are in close agreement with the hypothesis of Nelson[7] and Bose[8].

Meanwhile the intermediate disappeared, the two possible azetidinone diastereoisomers were formed; after 24 hours the evaluation of the ratio between the two isomers from the integrated area showed almost equal amount of cis (40%) and trans isomer (60%).

On the contrary, when the reaction was carried out in the probe at 60°, the spectra, recorded in time, showed the signals of **1a** and **2** together with those less intensive of **6a**. After a day cis and trans isomers were detected, in a ratio 20/80.

When the reaction was carried out between 4-methyl-benzal-4'-methylaniline (**1b**) and **2**, at 25°C, different results were obtained. After five minutes, the NMR spectrum of the reaction mixture showed signals which may account for the formation of two different intermediates **7b** and **6b** (Scheme 2). Together with the expected formation of **6b** (a sharp singlet at δ 7.96 (CHCl), two couples of coupled doublets at 7.10 (2H) and 7.47 (2H), at 7.27 (2H) and 7.34 (2H), a singlet at 7.09 (5H) and a singlet at 3.76 (CH_2), two singlets at 2.30 and 2.25 (2 CH_3)), the main component of the mixture seemed to be a nitrogen-charged species **7b** as it was hypothesized from the NMR signals lying at δ 9.22 (1H, s), 7.36 (2H, d) and 7.78 (2H, d), 8.77 (2H, d) and 7.49 (2H, d), 7.09 (5H, s, coincident with phenyl-group of **6b**), 3.84 (CH_2, s), 2.38 and 2.46 (2 CH_3, s).

The reported signals of **7b** are in accordance with the values reported by Olah and Kreienbuhl[11] concerning the chemical-shifts of azomethinic-hydrogens at protonated benzalanilines.

Meanwhile **6b** and **7b** disappeared from the reaction mixture, the two azetidinones isomers were formed; after two hours the reaction was complete and the ratio between trans and cis was 90/10.

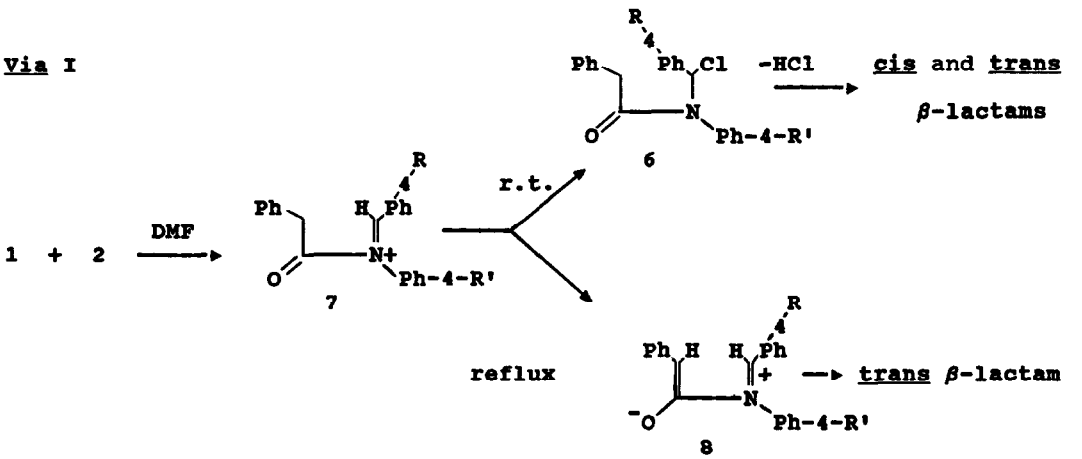
At 60 °C only the nitrogen-charged structure **7b** was detected and the trans azetidinone (**3b**) was the sole reaction product.

It is noteworthy that no isomerization of the pure cis or trans isomers was observed under the reaction conditions, or after addition of phenylacetic acid chloride at 25, 60 °C, or at reflux temperature.

Discussion

The reported NMR study on the formation of azetidinones suggests that intermediates develope along the way of the formation of azetidinones in DMF. In the Scheme 2, two proposed competitive mechanisms of the formation of cis and trans azetidinones via N-acylaminium ion I are shown; the cis/trans ratio is influenced by temperature and by the effect of the R-substituents at benzal-aniline.

Scheme 2



At reflux-temperature, the reaction seems to be governed by steric effects and only trans isomer is formed. The N-acyliminium ion intermediate 7 (described by Bohme et al.[5] in the reaction between cyanoacetyl chloride and imines) is stabilized by electron-donating substituents R. As Dreiding models suggest, a stable configuration of 7 is possible whereby the two 4-substituted-phenyl-groups are in cis configuration. To obtain some information about the geometry of this intermediate, a NOE difference study was performed at 25° C on **7b** in the reaction mixture of **1b** and **2**. Enanchement of signal at δ 9.22 (CH, s) together with the ortho aromatic protons was recorded by irradiation of the signal at 3.84 (CH_2, s). Enanchement of signal at δ 3.84 (CH_2, s) together with the ortho aromatic protons (8.77 δ; 2H, d) was also recorded by irradiation of the signal at δ 9.22 (CH, s). The reported results, in good agreement with the Dreiding model, support a configuration like **7** (Scheme 2). Any proton abstraction on this intermediate results in a (Z)-(E) double-bond stabilized zwitter-ion **8**. It gives rise to a conrotatory [2+2] cycloaddition[3,13] yielding the trans β-lactam isomer **3**.

On the contrary, at room temperature, the chlorobenzylacetanilide **6** is easily formed from **7**, by the stabilizing inductive effect of electron-

withdrawing substituents R. A dehydrohalogenation path takes place on **6**: the carbanion, generated in DMF[12], attacks the chiral benzylic-carbon, displacing the chloride ion and leading to the formation of both isomers **3** and **3'**. In the reaction mixtures of **1a** and **2** and of **1b** and **2**, at 25 °C, the intermediates **6a** and **6b** were detected by NMR analysis, and the cis/trans ratio was 40/60 and 10/90, respectively. In fact, the formation of **6**[7,8] is favoured by electron-withdrawing substituents R and by low temperatures, according to Bose's report about the stability of the 2-chloro-N-(α-chlorobenzyl)-acetanilide, formed in chloroform by mixing benzalaniline and chloroacetic acid chloride. This equilibrium, directly influenced by the temperature, lies at left at temperature higher than 40° C.

In this view the major amount of trans azetidinones at 25 °C, as well as the only trans formation at higher temperature, seem to arise from the zwitter-ion pathway, as shown in Scheme 2.

Therefore, on the basis of literature evidence and of the reported data, it seems to be possible hypothesize that, in the Staudinger reaction, β-lactams arise from two competitive mechanisms (Scheme 3). Base and temperature play a crucial role. The presence of a base pushes the reaction through the via **K**: a zwitterionic intermediate **8≡B** (planar or twisted[10,14,15,16] to minimize internal energy) can be formed and undergoing conrotatory [2+2] cyclization yields β-lactam. Steric and electrostatic effects, playing a role in the conformational preference of this reaction intermediate affect the stereochemistry of reaction. On the contrary, if base is not present, or it is added to reaction mixture after the other reactives, the via **I** is possible and the N-acyliminium ion **A≡7** is formed. Low temperatures allow the formation of the covalent compound **6** which, after dehydroalogenation, results in the same amount of cis and trans β-lactam. Otherwise, high temperatures, giving rise to the zwitterionic intermediate **8≡B**, yield cis or trans β-lactam. When temperature allows the two mechanisms, different amounts of cis and trans β-lactam are recovered.

A review (Table 2) of the stereochemical outcome of β-lactam cis/trans formation, selected from the literature, seems to support this hypothesis which lets to predict the stereochemical results.

1- When a free pair of electrons is available on the R_3 substituent, an electrostatic interaction is possible with the positive charge delocalized between carbon and nitrogen in **B** and the two hydrogens are pushed to the opposite sides; cis β-lactams are formed. This interaction is enhanced by electron-withdrawing and weakened by electron-donating R_1 and R_2 substituents; it affects the cis/trans ratio. If R_3 is an electron-donating bulky group the stereochemical results depend on the balance between steric repulsion and electrostatic attraction.

2- If R_3 is not able to form any electrostatic interaction, such as a phenyl-group, the ring closure is governed by steric hindrance and trans β-lactams are formed.

3- Stereochemical repulsion between substituents R_1 and R_3 seems to affect the formation of the zwitterionic intermediates B formed via acyliminium ion A more than the same intermediates B, formed via a ketene. An R_3 substituent, on an sp^3 carbanion, could produce more steric hindrance and a more effective electrostatic interaction with the positive charge, owing to a smaller bond-angle.

4- It was suggested[13] that β-lactam formation via ketene or via acyliminium ion could accommodate the different cis/trans ratio resulting from the different order of addition of amine base to the reaction mixture, as Bose et al.[7,8] reported.

5- Temperature and amine base affect the stereochemical results of this reaction. At lower temperatures, formation of an halideamide, like 6, is possible and results in cis and trans β-lactam mixtures. Amine base presence and higher temperatures inhibit halideamide formation[14]. It seems reasonable that also temperature increase weakens electrostatic interactions on the zwitterionic intermediate.

Scheme 3

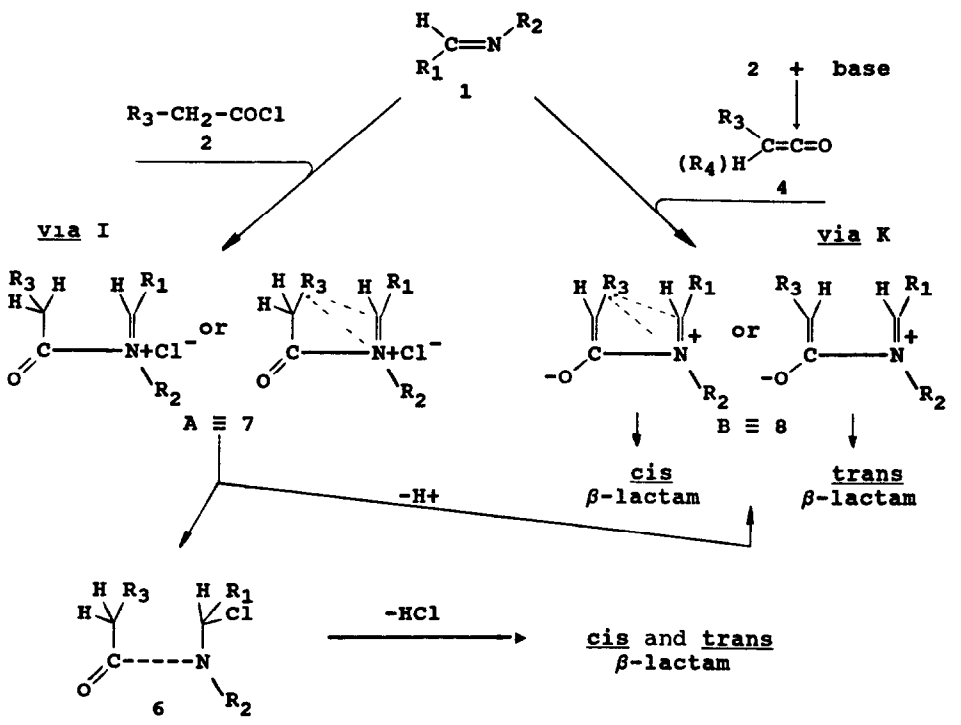


Table 2. β-lactam Formation as Reported in Literature: cis/trans Ratio=c/t. K=via Ketene, K*=via Ketene Formed in situ, I=via Acyliminium Ion[19].

R_4	R_3	R_2	R_1	K*+I	I	
H	CH_3	Ph	Ph	t	t	
H	Ph	Ph	Ph	t	t	
H	OMe	Ph	Ph	c/t=3	c/t=1.3	
H	OPh	Ph	Ph	c/t=6	c/t=0.7	
H	SPh	Ph	Ph	t		
H	CH_2OMe	Ph	Ph	t	t	
H	NH_2	Ph	Ph	c		a
H	Cl	Ph	Ph	t	t	
H	N_3	Ph	Ph	c/t=3	c/t=1.3	
H	N_3	4-BrPh	Ph	c/t=0.5		
H	N_3	Ph	4-NO_2Ph	c		
H	N_3	Ph	4-OMePh	c/t=0.7		
R_4	R_3	R_2	R_1	K	I	
Cl	CN	Ph	Ph	t (H and CN)		
t-Bu	CN	Ph	Ph	t "		b
Me	CN	Ph	Ph	t "		
H	Cl	Ph	Ph	t	c/t=1.1	
H	Cl	4-ClPh	2-NO_2Ph	c/t=0.5		
H	Cl	Ph	2-NO_2Ph	c/t=0 8	c/t=1	c
H	Cl	4-OMePh	4-NO_2Ph	t	c/t=1 1	
H	Cl	4-OMePh	4-OMePh	t	c/t=1	

K-Preformed ketenes were added to imine and nitrogen base solutions. **K***-Acyl halides were added to imine and nitrogen base solutions.
I-Nitrogen base was added to solutions of imines and acyl halides in a and b. In c no base was added

Experimental

The IR spectra were taken on a Perkin Elmer 399 spectrophotometer in chloroform. ^1H and ^{13}C NMR spectra (reported in δ) were recorded on a Bruker 270 MHz spectrometer with Me_4Si as internal reference. Mass spectra were obtained with a VG ZAB 2F mass-spectrometer (electron energy 70 eV, ion source temperature 250 °C). Melting points were determined with a Kofler apparatus and are uncorrected The purity of the compounds was checked by ascending TLC on Merck's precoated silica gel F-254 plates (0.25 mm) with fluorescent backing.

Formation of Azomethines. General procedure. 4-Substituted benzal-4'-substituted anilines were prepared by refluxing equimolecular amounts of 4-substituted benzaldehydes and 4-substituted anilines in dry benzene. The reaction was over in about 2h , when no more water was collected in the graduated water-separator apparatus. The solvent was removed by evaporation in vacuo and the residue was re-crystallized in ethanol.

1a. Anal. Calcd. for $C_{13}H_9BrClN$: C, 52.98; H, 3.05; N, 4.75. Found: C, 52.99; H, 3.04; N, 4.76. IR 1627 (C=N) cm^{-1}; ^1H NMR 8.38 (1H, s), 7.82 (2H, d), 7.50 (2H, d), 7.43 (2H, d), 7.08 (2H, d); ^{13}C NMR 159.11 (d), 150.57 (s), 137.62 (s), 134.39 (s), 131.94 (s), 132.21 (2C, d), 129.98 (2C, d), 129.11 (2C, d), 122.52 (2C, d); mass spectrum, m/e (M+) 295; mp 126-7 °C.

1b. Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.15; H, 7.24; N, 6.67. IR 1627 (C=N) cm^{-1}; ^1H NMR 8.41 (1H, s), 7.76 (2H, d), 7.25 (2H, d), 7.17 (2H, d), 7.12 (2H, d), 2.40 (3H, s), 2.35 (3H, s); ^{13}C NMR 159.55 (d), 149.57 (s), 141.63 (s), 133.74 (s), 115.22 (s), 129.71 (2C, d), 129.44 (2C, d), 128.68 (2C, d), 120.78 (2C, d), 21.62 (q), 20.97 (q); mass spectrum, m/e (M+) 209; mp 91-2 °C.

1c. Anal. Calcd. for $C_{13}H_{11}N$: C, 86.16; H, 6.12; N, 7.73. Found: C, 86.20; H, 6.10; N, 7.75. IR 1626 (C=N) cm^{-1}; ^1H NMR 8.49 (1H, s), 7.95 (2H, d), 7.51 (3H, d+t), 7.43 (1H, t), 7.27 (2H, t), 7.26 (2H, d); ^{13}C NMR 160.00 (d), 152.00 (s), 137.00 (s), 131.30 (d), 129.06 (4C, d), 128.70 (2C, d), 125.80 (d), 120.80 (2C, d); mass spectrum, m/e (M+) 181; mp 54-5 °C.

1d. Anal. Calcd. for $C_{14}H_{13}N$: C, 86.11; H, 6.71; N, 7.17. Found: C, 86.17; H, 6.69; N, 7.15. IR 1626 (C=N) cm^{-1}; ^1H NMR 8.34 (1H, s), 7.75 (2H, d), 7.35 (1H, t), 7.21 (2H, d), 7.20 (2H, t), 7.19 (2H, d), 2.39 (3H, s); ^{13}C NMR 160.30 (d), 152.00 (s), 141.00 (s), 133.00 (s), 129.40 (2C, d), 129.11 (2C, d), 128.89 (2C, d), 125.78 (d), 120.90 (2C, d), 21.62 (q); mass spectrum, m/e (M+) 195; mp 41-2 °C.

1e. Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.42; H, 4 88; N, 5.70. Found: C, 68.46; H, 4.90; N, 5.69. IR 1628 (C=N), cm^{-1}; ^1H NMR 8.30 (1H, s), 7.78 (2H, d), 7.28 (2H, d), 7.07 (2H, d), 6.93 (2H, d), 3.83 (3H, s); ^{13}C NMR 162.51 (s), 159.79 (s+d), 150 89 (s), 131.03 (s), 130.60 (2C, d), 129.15 (2C, d), 122.14 (2C, d), 114.28 (2C, d), 55.40 (q); mass spectrum, m/e (M+) 245; mp 93-4 °C.

Substituted trans 1,3,4-triphenylazetidin-2-ones. General procedure A[17].

To 10 ml of stirring DMF, 2 mmol of phenylacetyl chloride and 2 mmol of azomethine were added and the solution was heated to reflux for 2h. The reaction mixture, cooled and diluted with 50 ml of water, was extracted with 25 ml of dichloromethane. The organic layer, dried and evaporated *in vacuo*, afforded an oil or a crystalline residue which, after crystallization from ethanol, afforded β-lactams **3**. In the mother liquors aldehydes and phenylacetanilides were also detected.

3a. Anal. Calcd. for $C_{21}H_{15}BrClNO$: C, 61.11; H, 3.66; N, 3.39. Found: C, 61.05; H, 3.64; N, 3.38 IR 1752 (C=O) cm^{-1}; ^1H NMR 7.39 (2H, d), 7.37 (2H, d), 7.33 (5H, s), 7.32 (2H, d), 7.21 (2H, d), 4.91 (1H, d; J_{trans}=2.5 Hz), 4.26 (1H, d; J_{trans}=2.5 Hz), ^{13}C NMR 165 27 (s), 140.11 (s), 136.19 (s), 135.59 (s), 132.21 (s), 129.71 (2C, d), 129.17 (2C, d), 128.18 (2C, d), 127.37 (2C, d), 127.28 (2C, d), 127.00 (2C, d), 123.95 (d), 118.17 (s), 65.51 (d), 63.16 (d); mass spectrum, m/e (M+) 412; mp 155-6 °C.

3b. Anal. Calcd. for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.41; H, 6.45; N, 4.29. IR 1752 (C=O) cm^{-1}; ^1H NMR 7.37 (5H, s), 7.31 (2H, d), 7.29 (2H, d), 7 22 (2H, d), 7.09 (2H, d), 4.92 (1H, d; J_{trans}=2.5 Hz), 4.26 (1H, d; J_{trans}=2.5 Hz), 2.38 (3H, s), 2.30 (3H, s); ^{13}C NMR 165.38 (s), 138.42 (s), 135.04 (s), 134.88 (s), 134.54 (s), 133.52 (s), 129.87 (2C, d), 129.49 (2C, d), 128.94 (2C, d), 127.75 (2C, d), 127.42 (2C, d), 125.79 (2C, d), 117.09 (d), 65.07 (d), 63.51 (d), 21.13 (q), 20 86 (q); mass spectrum, m/e (M+) 327, mp 121-2 °C.

3c. Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.31; H, 5.70; N, 4.70. IR 1751 (C=O) cm^{-1}; ^1H NMR 7.39 (5H, s), 7.41-7.33 (5H, m), 7.33 (2H, t), 7.26 (2H, t), 7.06 (1H, t), 4.96 (1H, d; J_{trans}=2.5 Hz), 4.28 (1H, d; J_{trans}=2.5 Hz); ^{13}C NMR 165.59 (s), 137.54 (s), 137.52 (s), 134.71 (s), 129.32 (2C, d), 129.08 (4C, d), 128.67 (d), 127.91 (2C, d), 127.47 (2C, d), 125.89 (2C, d), 124.04 (d), 117.22 (d), 65.13 (d), 63.71 (d); mass spectrum, m/e (M+) 299; mp 130-1 °C[18].

3d. Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.26; H, 6.13; N, 4.45. IR 1747 (C=O) cm^{-1}; ^1H NMR 7.27 (2H, d), 7.26 (5H, s), 7.20 (2H, d), 7.18 (2H, d), 7.12 (2H, t), 6.96 (1H, t), 4.83 (1H, d; J_{trans}=2.5 Hz), 4.17 (1H, d; J_{trans}=2.5 Hz), 2.27 (3H, s); ^{13}C NMR 165.69 (s), 138.55 (s), 137.55 (s), 134.83 (s), 134.56 (s), 129.98 (2C, d), 129.03 (4C, d), 127.86 (2C, d), 127.47 (2C, d), 125.88 (2C, d), 123.99 (d), 117.24 (d), 65.19 (d), 63.67 (d), 21.20 (q); mass spectrum, m/e (M+) 313; mp 115-6 °C[18].

3e. Anal. Calcd. for $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.99; N, 3.85. Found: C, 72.70; H, 5.01; N, 3.84. IR 1751 (C=O) cm^{-1}, ^1H NMR 7.32 (5H, s), 7.30 (2H, d), 7.28 (2H, d), 7.20 (2H, d), 6.91 (2H, d), 4.88 (1H, d; J_{trans}=2.5 Hz), 4.26 (1H, d; J_{trans}=2.5 Hz), 3.80 (3H, s); ^{13}C NMR 165.54 (s), 159.93 (s), 135.91 (s), 134.77 (s), 134.50 (s), 129 05 (2C, d), 128.95 (2C, d), 128.79 (d), 127.86 (d), 127.29 (2C, d), 127.14 (2C, d), 118.33 (2C, d), 114.68 (2C, d), 65.34 (d), 63.48 (d), 55.52 (q), mass spectrum, m/e (M+) 363; mp 127-8 °C.

Substituted cis 1,3,4-triphenylazetidin-2-ones. General procedure A'.

To 10 ml of stirring DMF, 2 mmol of phenylacetyl chloride and 2 mmol of azomethine were added and the solution kept at room temperature for 2 days. The reaction mixture, diluted with 50 ml of water, was extracted with 25 ml of dichloromethane. The organic layer, dried and evaporated *in vacuo*, afforded an oil residue which, analyzed on silica gel plates using as eluent a chloroform-carbon tetrachloride (1:1 vv) mixture, afforded the **3**, **3'** β-lactams, aldehydes and phenylacetanilides Cis β-lactams were recrystallized from ethanol.

3'a. Anal. Calcd. for $C_{21}H_{15}BrClNO$. C, 61.11, H, 3.66, N, 3.39. Found: C, 61.05; H, 3.64; N, 3.38. IR 1752 (C=O) cm^{-1}; ^1H NMR 7.40 (2H, d), 7.27 (2H, d), 7.10 (4H, m), 7.09 (2H, d), 7.01 (1H, t), 6.97 (2H, d), 5.40 (1H, d; J_{Cis}=6.2 Hz), 5.03 (1H, d; J_{Cis}=6.2 Hz) ; ^{13}C NMR 165.32 (s), 136.40 (s), 133.98 (s), 132.21 (s), 131.44 (s), 128.72 (2C, d), 128.62 (2C, d), 128.40 (6C, d), 127.58 (2C, d), 118.71 (s), 116.95 (d), 60.61 (d), 59.83 (d); mass spectrum, m/e (M+) 412; mp 160-1 °C.

3'b Anal. Calcd. for $C_{23}H_{21}NO$· C, 84 37, H, 6.47; N, 4.28. Found: C, 84.35; H, 6.46; N, 4.28 IR 1752 (C=O) cm^{-1}, ^1H NMR 7.29 (2H, d), 7.09 (2H, d), 7.08 (5H, s), 6.91 (2H, d), 6.90 (2H, d), 5 40 (1H, d, J_{Cis}=6.2 Hz), 4.96 (1H, d; J_{Cis}=6.2 Hz), 2.30 (3H, s), 2.19 (3H, s); ^{13}C NMR 163.36 (s), 137 49 (s), 134.90 (s), 134 62 (s), 133 57 (s), 129.54 (2C, d), 128.89 (4C, d), 128.35 (s), 128.07 (2C, d), 127.09 (4C, d), 117.18 (d), 60.22 (d), 60.17 (d), 21.07 (q), 20.91 (q); mass spectrum, m/e (M+) 327, mp 201-2 °C.

3'c. Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.48. Found: C, 84.31; H, 5.70; N, 4.70. IR 1751 (C=O) cm^{-1}; ^1H NMR 7.42 (2H, d), 7.30 (2H, d), 7.12-05 (11H, m), 5.47 (1H, d; J_{Cis}=6.2 Hz), 5.01 (1H, d; J_{Cis}=6.2 Hz); ^{13}C NMR 165.65 (s), 137.71 (s), 134.39 (s), 132.10 (s), 129.11 (2C, d), 128.90 (2C, d), 128 24 (2C, d), 128 08 (2C, d), 127.87 (d), 127 15 (4C, d), 124.08 (d), 117 24 (d), 60.36 (2C, d), mass spectrum, m/e (M+) 299; mp 182-3 °C[18].

3'd. Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.25; H, 6.12; N, 4.48. IR 1747 (C=O) cm^{-1}; ^1H NMR ; 7.41 (2H, d), 7.26 (2H, d), 7.08 (5H, m), 6.94 (2H, d), 6.94 (2H, d), 6.93 (2H, d), 5.43 (1H, d; J_{cis}=6.2 Hz), 4.92 (1H, d; J_{cis}=6.2 Hz), 2.18 (3H, s); ^{13}C NMR, 162.58 (s), 137.45 (s), 135.50 (s), 132.65 (s), 130.50 (s), 129.06 (2C, d), 128.92 (2C, d), 128.07 (2C, d), 127.74 (s), 127.09 (4C, d), 123.99 (2C, d), 117.24 (d), 60.25 (2C, d), 20.85 (q) mass spectrum, m/e (M+) 313; mp 142-3 °C.

3'e. Anal. Calcd. for $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.99; N, 3.85. Found: C, 72.71; H, 4.97; N, 3.87. IR 1752 (C=O) cm^{-1}; ^1H NMR ; 7.35 (2H, d), 7.24 (2H, d), 7.13-7.04 (5H, m), 6.96 (2H, d), 6.66 (2H, d), 5.41 (1H, d; J_{cis}=6.2 Hz), 5.01 (1H, d; J_{cis}=6.2 Hz), 3.70 (3H, s); ^{13}C NMR 159.29 (s), 132.02 (s), 130.91 (s), 129.11 (2C, d), 129,78 (2C, d), 128.36 (2C, d), 128.16 (2C, d), 127.20 (s), 125.78 (s), 121.29 (s), 119.28 (2C, d), 113.78 (2C, d), 105.17 (s), 60.50 (d), 60.13 (d), 55.11 (q); mass spectrum, m/e (M+) 363; mp 158-9°C.

Phenylacetanilide. Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.57; H, 6.18; N, 6.64. IR 3300 (NH), 1680 (C=O) cm^{-1}; ^1H NMR 7.42-7.23 (9H, m), 7.11 (2H, bt), 3.72 (2H, s); ^{13}C NMR 169.17 (s), 137.55 (s), 134.37 (s), 129.49 (2C, d), 129.17 (2C, d), 128.88 (2C, d), 127.63 (2C, d), 124.42 (d), 119.81 (d), 44.74 (t); mass spectrum, m/e (M+) 211; mp 117-8 °C.

Substituted 1,3,4-triphenylazetidin-2-ones. General procedure B.

The solution of 4-substituted-benzal-4'-substituted anilines (0.1 mmol in 0.5 ml DMF d_7) was recorded and mixed with a solution of phenylacetic acid chloride **2** (0.1 mmol in 0.5 ml DMF d_7). The reaction mixture was quickly examined by NMR spectrometer and an ^1H NMR was recorded every ten minutes. The reaction was carried out at 25 and 60 °C.

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