Reaction of *N*-Trimethylsilyl Benzil Monoimine with Simple Lithium Ester Enolates. A Synthetic Tool for the Regioselective One-Pot Preparation of Novel Polyfunctional Pyrrolines

Benito Alcaide* and Julián Rodríguez-López
Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Ciudad Universitaria, 28040-Madrid, Spain

Sequential treatment of benzil with lithium hexamethyldisilylamide and simple α-lithiated esters leads, in a regioselective one-pot process, to the polyfunctional pyrrolines(**4**)–(**8**), depending on the nature of the enolate and on the experimental conditions. A reasonable explanation for the observed results is discussed. In addition, the reaction of 2,5-dihydro-5-hydroxy-4,5-diphenyl-2-oxo-1*H*-pyrrole-3-carbonitrile with sodium hydroxide has been reinvestigated and the structure of the previously described product corrected.

Several years ago we became interested in the reaction of imino ketones[1,2] and related bifunctional electrophiles[3,4] with ester enolates in order to explore methods for the synthesis of useful, simple polyfunctional compounds. Within the framework of this investigation, we have already reported the reaction of *N*-aryl α-imino ketones and simple lithium ester enolates to give β-hydroxy-γ-imino esters in a totally site-selective addition to the carbonyl group,[1] and the reaction between various *N*-(α-methoxyphenacyl)anilines (synthetic equivalents of the related phenylglyoxal anils) and methyl lithioisobutyrate which yielded addition products by attack at either the carbonyl or the imino group through a regiocontrolled process.[3] In this paper we describe the unique behaviour of *N*-trimethylsilyl benzil monoimine (**1**) in its reaction with lithium ester enolates, which has allowed the synthesis of some novel polyfunctional pyrrolines (**4**)–(**8**) to be achieved in a simple and regioselective fashion. Among different pyrrolines prepared, compounds (**5**), (**6**), and (**8**) are of particular interest. Five-membered monocyclic *N*-monoacylimines related to structure (**5**), and their acyliminium ions have been proposed as reactive intermediates in various useful processes.[5] The only example of an isolable acylimine of this type is 3-phenylisoindol-1-one, although a large number of precursors of isoindol-1-ones have been described.[6] On the other hand, compounds (**5b**), (**5c**), (**5d**), and (**6**) may be suitable synthons for the generation of the corresponding antiaromatic 2-azacyclopenta-2,4-dienones (**9**),† and compounds (**8**) for the preparation of the related azafulvenes (**10**).[8] These types of structures have aroused interest from both the synthetic and the theoretical standpoints.

Results and Discussion

The starting *N*-silylated α-imino ketone (**1**)‡ was prepared by reaction of benzil with lithium hexamethyldisilylamide (LHMDS) in dry tetrahydrofuran (THF)–hexane at 0 °C according to a known procedure for simple *N*-silylimines.[9] Since purification of this compound led only to decomposition products, it was used *in situ* as a THF–hexane solution in order to investigate its reactivity. Thus the intermediacy of compound (**1**) was presumed on the basis of the products obtained upon treatment of the THF solution with α-lithiated esters. Additional chemical evidence for the formation of compound (**1**) was obtained by its stereoselective reduction to *erythro*-2-amino-1,2-diphenylethanol with lithium aluminium hydride (LAH). The synthesis of this amino alcohol has been attained by catalytic hydrogenation of benzoin oxime.[10] It is noteworthy that this stereochemical result is opposite to that previously described by us for the LAH reduction of *N*-aryl benzil monoimines.[11]

By reaction of silylimine (**1**) with excess of ester enolates (**2**) (2 mol equiv.), generated *in situ* from the corresponding carboxylic esters and lithium di-isopropylamide (LDA), we have obtained in a straightforward manner, the *N*-silylated β-hydroxy-γ-imino ester (**3**) and the polyfunctional pyrrolines (**4**)–(**8**), depending on the nature of the enolate and on the experimental conditions (temperature and reaction time). Thus, at −78 °C and independently of the reaction time, enolate (**2a**) yielded compound (**3**) while enolates (**2b**) and (**2c**) gave, respectively, compounds (**5b**) and (**5c**) exclusively under the same conditions. Along with compound (**5c**) a *ca.* 10% yield of compound (**5d**) was detected in the reaction mixture residue (^{1}H NMR spectrometry). Otherwise, partial desilylation of (**5c**) to (**5d**) is observed during chromatographic purification of the crude product, compound (**5d**) being obtained in 21% yield. This transformation of the siloxane (**5c**) into the alcohol (**5d**) has allowed us to assign the same relative stereochemistry to both compounds (see below). When the reaction temperature was raised to room temperature, in the reaction of enolate (**2a**), progressive formation of compound (**4**) was observed, along with some of compound (**3**), the relative proportion of the former increasing with time. A nearly quantitative final yield of crude product (**4**) was obtained, after 22 h at room temperature; as a single diastereoisomer whose configuration has not been determined yet. In the reaction of enolate (**2b**), compound (**8a**) was obtained as the main product after 50 min at room temperature; longer reaction times afforded a mixture of compounds (**6a**) and (**8b**) with the latter being the first product formed in the reaction. From enolate (**2c**) a mixture of compounds (**6b**), (**6c**), and (**7**) was obtained, with the first being the main reaction product. Even in the presence of a larger excess of enolate (**2c**) none of the compound arising from addition of two molecules of enolate [related to compound (**8**)]

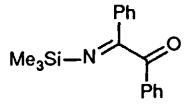
† Very recently, Gaviña *et al.* have generated the elusive antiaromatic 2-azacyclopenta-2,4-dienone from an insoluble polymeric precursor, thus demonstrating its free existence in solution. The liberated intermediate can act either as a diene or as a dienophile in Diels–Alder reactions: see ref. 7.

‡ Compound (**1**) is the first reported example of an *N*-silylated α-imino ketone, although the related benzil di-imine has been reported. See: G. Tuchtenhagen and K. Rühlmann, *Justus Liebigs Ann. Chem.*, 1968, **711**, 174.

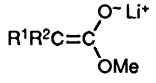
Table. Reaction conditions and yield of products (3)–(8) obtained in the reaction of silylimine (1) with enolates (2).

Entry	Enolate	Reaction conditions	Product[a]	Yield[c]
1	(2a)	−78 °C, 15 min	(3)	>95
2	(2a)	−78 °C, 15 min; room temp., 22 h	(4)	60
3	(2b)	−78 °C, 15 min	(5b)	70
4	(2b)	−78 °C, 15 min; room temp., 50 min	(8a)[b]	40
5	(2b)	−78 °C, 15 min; room temp., 3 days	(8b), (6a)	38, 40
6	(2c)	−78 °C, 15 min	(5c), (5d)	45, 21
7	(2c)	−78 °C, 15 min; room temp., 3 days	(6b), (6c), (7)	35, 40[d]

[a] The products were isolated by flash column chromatography in all cases (hexane–EtOAc, 4:1 unless otherwise stated) except for compound (3). [b] Compound (5b) was obtained as a by-product in 17% yield. [c] Yields are for pure isolated white solids with correct analytical data, except for compound (3) (viscous, pale yellow oil) estimated by ^{1}H NMR spectrometry in the crude product. [d] Yield (40%) refers to the mixture of products (6c) and (7).

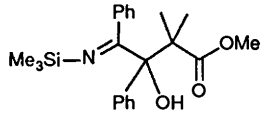


(1)

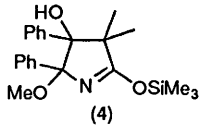


(2)

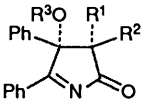
a; $R^1 = R^2 = Me$
b; $R^1 = R^2 = H$
c; $R^1 = H$, $R^2 = Me$



(3)

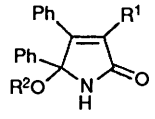


(4)



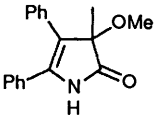
(5)

a; $R^1 = R^2 = Me$, $R^3 = H$
b; $R^1 = R^2 = H$, $R^3 = SiMe_3$
c; $R^1 = H$, $R^2 = Me$, $R^3 = SiMe_3$
d; $R^1 = R^3 = H$, $R^2 = Me$

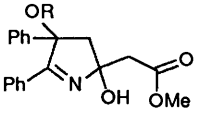


(6)

a; $R^1 = H$, $R^2 = SiMe_3$
b; $R^1 = Me$, $R^2 = SiMe_3$
c; $R^1 = R^2 = Me$

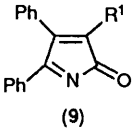


(7)



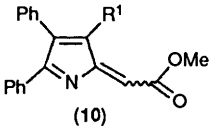
(8)

a; R = $SiMe_3$
b; R = H



(9)

a; R = H
b; R = Me



(10)

could be detected. These results and the reaction conditions are summarized in the Table.

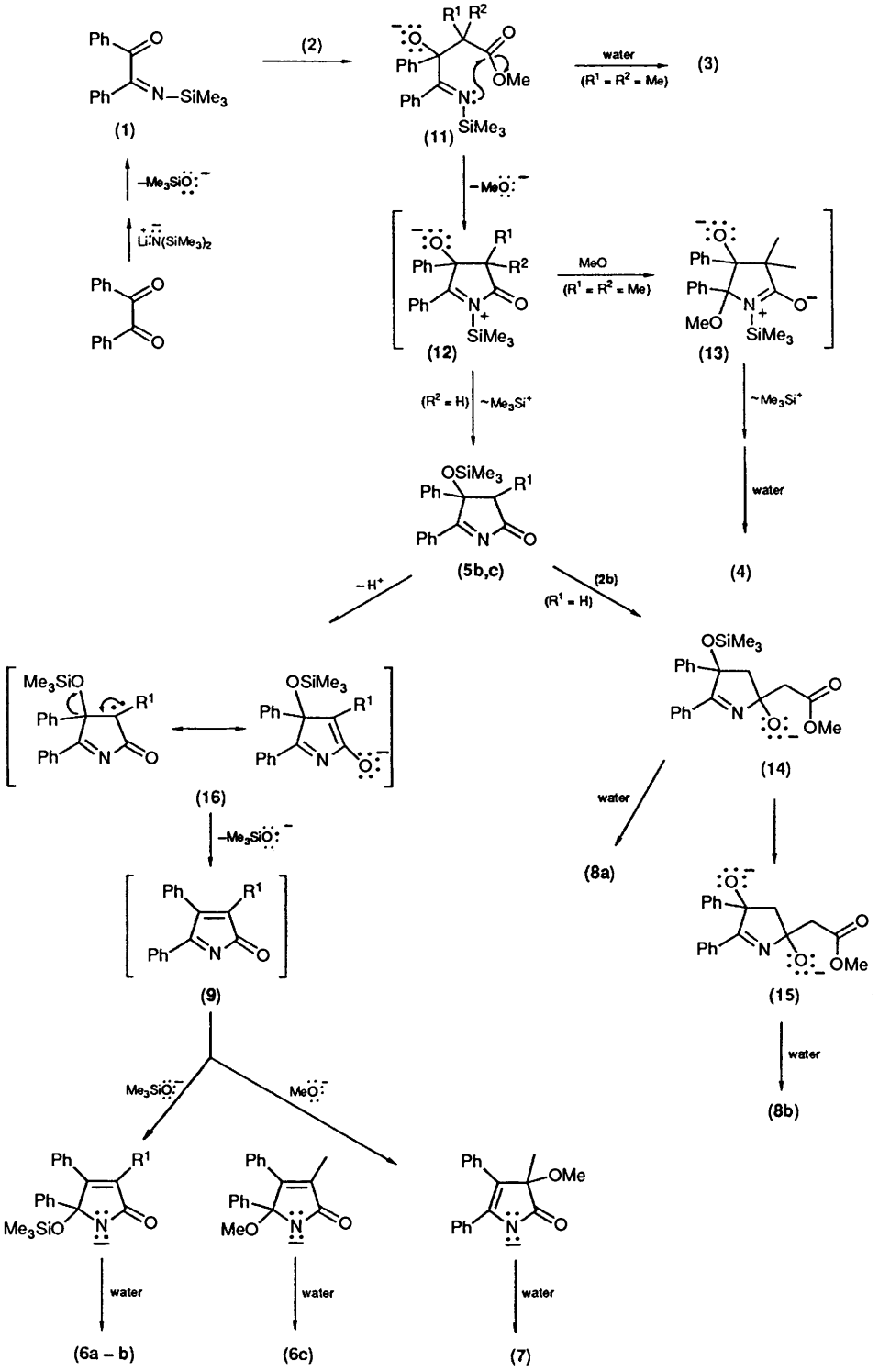
The overall reaction may be rationalized as shown in Scheme 1. Initial addition of the enolate to the carbonyl group of imino ketone (1), at −78 °C, gave the alkoxide (11) which immediately cyclized to zwitterion (12) by an intramolecular *N*-acylation process when enolates (2b) and (2c) were used. This *N*-trimethylsilyliminium salt (12) could act as the *O*-silylating agent to afford compounds (5b) and (5c). When $R^1 = R^2 = Me$ the higher steric crowding prevented cyclization of the corresponding alkoxide (11) at this temperature, and instead yielded open-chain product (3) after quenching with water. When the reaction temperature was raised above −78 °C the formation of compound (4) from enolate (2a) was observed, and may be interpreted as occurring by conjugate addition of methoxide to the *N*-acyliminium group of zwitterion (12) followed by a 1,3-nitrogen-to-oxygen shift of the trimethylsilyl group in intermediate (13). Formation of products (6a) and (8) from enolate (2b), upon raising the temperature, may be accounted for through intermediary of the corresponding compound (5b). Addition of a second molecule of enolate to the carbonyl group of compound (5b) gave the alkoxide (14) which, besides yielding the alcohol (8a), can also form the dialkoxide (15) by desilylation, probably by methoxide, which afforded diol (8b) after quenching. In a separate experiment, it was observed that reaction of intermediate (5b) with an excess of enolate (2b) under identical reaction conditions led to compound (8a) in moderate yield (38%).* Alternatively, base-induced elimination of the trimethylsilyl oxide group in (5b), *via* anion (16; $R^1 = H$) presumably through an *E*1cB mechanism, could afford aza-annulenone (9a) as an unstable intermediate,[7] which would add Me_3SiO^- to the C=N group to give finally the Δ^3-pyrroline (6a).† On the other hand, formation of products (6b), (6c), and (7) [derived from enolate (2c)] could have a similar origin *via* the corresponding aza-annulenone (9b). Along with the pyrroline (6b), isolation of compounds (6c) and (7), which represent, respectively, the normal and conjugated addition products to the 1-azadiene moiety of (9b), clearly indicates participation of the aza-annulenone in the process.

It is very significant that such a marked difference in reactivity was observed between various enolates studied in their reactions with the silylimine (1) at room temperature. Although this finding could be accounted for in terms of the nucleophilicity and steric crowding of the enolate, it is difficult at present to rationalize satisfactorily the dependence of the reaction pattern on the nature of the enolate.

Two stereochemical aspects of the whole process shown in

* To the best of our knowledge this is the first reported addition of an enolate to the carbonyl group in *N*-acylimines. Addition to the imino group in these compounds or their precursors is one of the significant α-amidoalkylation reactions (see ref. 5).

† Treatment of compound (5b) with LDA (1.2 mol equiv.) in THF solution gave (6a) in moderate yield.



Scheme 1.

Scheme 1 are noteworthy. First, a totally stereoselective reaction is observed from methyl lithiopropionate (**2c**). The relative stereochemistry of intermediate (**5c**) [and hence of (**5d**)] was based on NOE and NOESY experiments. This latter experiment showed an NOE on both the C(3)-H and the C(3)-Me signals when the trimethylsilyl oxide group was irradiated. However, a difference NOE experiment gave a 7% enhancement of the C(3)-H signal relative to the C(3)-Me, allowing the assignment of configuration as $3R^*,4S^*$. Second, compounds (**8**) were apparently a mixture of diastereoisomers in the relative proportions 62:38 for (**8a**) and 53:47 for (**8b**), when analysed in solution (^1H and ^{13}C NMR spectrometry) under standard conditions. However, both products melt within a narrow range and are homogeneous on TLC. On the other hand, when the ^1H NMR spectrum of compound (**8a**) was quickly recorded a 75:25 isomeric proportion was observed; this evolved with time to the equilibrium mixture indicated before. This phenomenon was not observed for dihydroxy

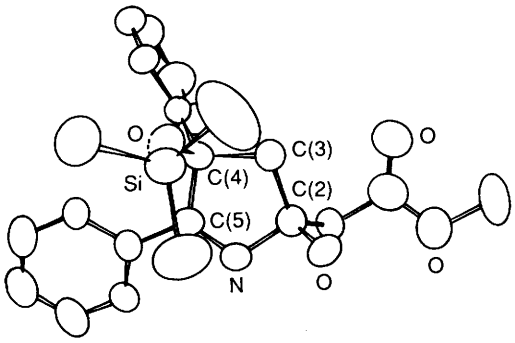
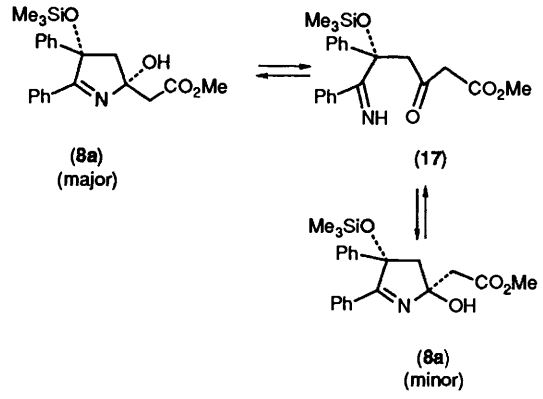


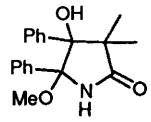
Figure. ORTEP drawing of compound (**8a**).

compound (**8b**), probably because to its lower solubility which prevented a rapid recording of the spectrum. From these observations it may be deduced that compound (**8a**) [and very probably compound (**8b**)] is a single diastereoisomer in the solid state, which corresponds to the major isomer. X-Ray analysis of compound (**8a**) established its relative stereochemistry as 2*R**,4*S** (Figure).* Moreover, comparison of the powder X-ray analysis with that of the crystal for this compound suggested a homogeneous sample. However, it is difficult to understand the exclusive obtainment of a single stereoisomer on account of the origin of compounds (**8**), which are formed through a process, for which *a priori* appreciable stereoselectivity is not expected. These facts could be reasonably accounted for through a rapid isomerization equilibrium in solution through the open-chain tautomer (**17**) as shown in Scheme 2. The major diastereoisomer must be considerably more stable in the solid state and therefore only one isomer is observed upon crystallization or removal of the solvent. It has been reported that addition of primary and secondary amides to aldehydes and ketones leads to α-hydroxyalkyl amides in an equilibrium process, unless the carbonyl compound is very reactive or the labile C–N bond is contained in a five- or six-membered ring.[5,12]

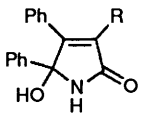


Scheme 2.

In addition, several transformations of some of the prepared products have been studied. Thus, treatment of the silylimine (**3**) in refluxing anhydrous methanol gave compound (**18**) as a single diastereoisomer in 80% yield. Its formation may be accounted for by intramolecular *N*-acylation followed by addition of methanol to the C=N bond in the resulting pyrrolinone (**5a**). Furthermore, compound (**5a**) was quantitatively obtained from compound (**18**) by demethanolation with Pd/C in refluxing benzene. On the other hand, desilylation of compounds (**6a**) and (**6b**) was easily achieved by reaction with anhydrous methanol, and gave compounds (**19**) in nearly quantitative yield.



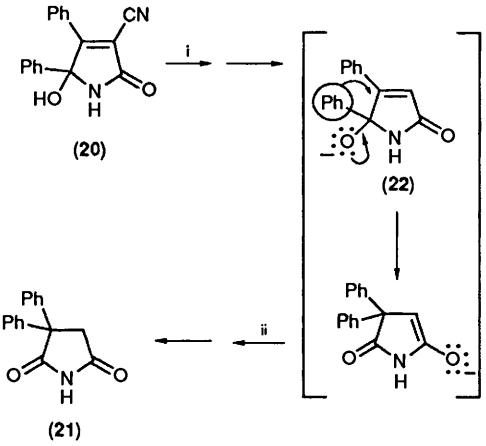
(18)



(19)

a; R = H
b; R = Me

The synthesis of compound (**19a**) has been previously reported[13] by treatment of compound (**20**)[14] with base. However, the m.p. of our product is in disagreement with that reported by others.[13] We have reinvestigated this reaction under the same experimental conditions as those reported,[13] and have assigned a structure of 3,3-diphenylsuccinimide (**21**) to the previously obtained product on the basis of spectral data and by comparison with an authentic sample.[15] Formation of imide (**21**) may be accounted for as shown in Scheme 3, which involves a conjugated benzil–benzylic acid-like rearrangement in the alkoxide intermediate (**22**) formed from the pyrrolinone (**20**) by hydrolysis and subsequent decarboxylation.[16]



Scheme 3. *Reagents and conditions:* i, OH^-, heat; ii, H^+.

In summary, on changing the *N*-aryl for an *N*-trimethylsilyl group in benzil monoimines both the reactivity and the nature of the products are greatly affected. Moreover, this reaction provides a simple method for obtaining, in a straightforward manner, a variety of polyfunctional pyrrolines, some of them having an interesting juxtaposition of functionality.

Experimental

M.p.s were determined in open capillaries on a Büchi 512 apparatus, and are uncorrected. IR spectra were recorded with a Perkin-Elmer 781 grating spectrophotometer. ^1H NMR were recorded with a Varian T-60A (60 MHz) or with a Varian VXR 300S (300 MHz) spectrometer, with $SiMe_4$ as internal standard. ^{13}C NMR spectra were recorded with a Varian FT-80 (20.15 MHz) spectrometer. ^1H and ^{13}C NMR, chemical shifts are reported downfield from $SiMe_4$. Mass spectra were determined with a Varian MAT 711 instrument. Elemental analyses were

* X-Ray analysis was performed by Dr Monge and Miss V. Pérez-García (Instituto de Química Inorgánica 'Elhuyar'). Full details will be published in due course. We thank the aforementioned workers for communicating their results to us.

performed at the Instituto de Química Bio-Orgánica, CSIC, Barcelona. Flash chromatography was performed using Merck silica gel (250–400 mesh). THF was dried over sodium–benzophenone ketyl and was freshly distilled before use. Hexamethyldisilazane and di-isopropylamine were distilled from calcium hydride and stored over molecular sieves (4 Å). Standardized (1.6M) butyl-lithium in hexane was obtained from Aldrich Chemical Co. Methyl acetate, methyl propionate, and methyl isobutyrate were available through commercial sources and were distilled from sodium carbonate prior to use. All reactions requiring anhydrous conditions were performed under a positive atmosphere of nitrogen in oven-dried glassware.

Preparation of N-*Trimethylsilyl Benzil Monoimine* (**1**).—Lithium bis(trimethylsilyl)amide (LHMDS) (5.7 mmol) was prepared from 1,1,1,3,3,3-hexamethyldisilazane (1.2 ml, 5.9 mmol) and butyl-lithium (1.6M solution in hexane) (3.6 ml, 5.7 mmol) in dry THF (6 ml) at room temperature for 30 min. To this solution, cooled to 0 °C, was added a solution of benzil (1.0 g, 4.8 mmol) in dry THF (5 ml). The mixture was stirred at this temperature for 30–40 min and the resulting solution of reagent (**1**) was used directly in the following one-pot reactions.

LAH Reduction of Monoimine (**1**).—*Synthesis of* erythro-2-*amino*-1,2-*diphenylethanol.* To a cooled (0 °C) suspension of LAH (181 mg, 4.8 mmol) in anhydrous THF (4 ml) was added a solution of freshly prepared monoimine (**1**) (2.4 mmol) obtained from benzil (500 mg, 2.4 mmol) as described above. The resulting mixture was stirred at 0 °C for 30 min. Then, diethyl ether (50 ml) was added and, after hydrolysis with the minimum amount of water, aluminium salts were filtered off. From the resulting filtrate the title compound crystallized (380 mg, 75%) as a white crystalline solid, m.p. 163–165 °C (from EtOAc) (lit.,[10] 163 °C).

One-Pot Preparation of Functionalized Pyrrolines from Benzil and Lithium Ester Enolates (**2**). *General Procedure.*—LDA (10.5 mmol) was prepared from di-isopropylamine (1.5 ml, 10.5 mmol) and butyl-lithium (6.5 ml of a 1.6M solution in hexane; 10.5 mmol) in dry THF (10 ml). To this solution cooled to − 78 °C was added a solution of the appropriate ester (9.5 mmol) in THF (3.5 ml) (the temperature was kept below −70 °C) and the mixture was stirred for 15 min, and was then treated with freshly prepared silylimine solution (4.8 mmol). The resulting solution was stirred at the temperature and time indicated in the Table. Finally, the reaction was worked up by dilution of the reaction mixture with diethyl ether (100 ml) and washing successively with water (×2) and brine (×1). The organic layer was dried over anhydrous magnesium sulphate and the solvent was then removed under reduced pressure. In most cases purification was effected by flash chromatography on silica gel.

Methyl 3-*hydroxy*-2,2-*dimethyl*-3,4-*diphenyl*-4-(*trimethylsilylimino*)*butyrate* (**3**). ν_{max}(film) 3 460 (OH), 1 690 (C=O), and 1 605 cm^{-1}; δ_H(60 MHz; $CDCl_3$) −0.60 (9 H, s, $SiMe_3$), 1.10 (3 H, s, 2-Me), 1.35 (3 H, s, 2-Me), 3.63 (3 H, s, OMe), 5.17 (1 H, s, 3-OH), and 6.50–7.43 (10 H, m, Ph).

3,4-*Dihydro*-2-*methoxy*-4,4-*dimethyl*-2,3-*diphenyl*-5-*trimethylsilyloxy*-3H-*pyrrol*-3-*ol* (**4**). M.p. 113–115 °C (from hexane) (Found: C, 68.7; H, 7.6; N, 3.4. $C_{22}H_{29}NO_3Si$ requires C, 68.89; H, 7.62; N, 3.65%); ν_{max}(KBr) 3 480 (OH) and 1 610 cm^{-1} (C=N); δ_H(60 MHz; $CDCl_3$) 0.33 (9 H, s, $SiMe_3$), 0.53 (3 H, s, 4-Me), 1.03 (3 H, s, 4-Me), 3.43 (3 H, s, OMe), 4.00 (1 H, s, OH), 7.13–7.30 (8 H, m, ArH), and 7.57–7.77 (2 H, m, ArH); δ_C($CDCl_3$) 2.0 ($SiMe_3$), 14.8 (4-Me), 24.0 (4-Me), 50.0 and 52.3 (OMe and C-4), 88.3 (C-3), 118.5 (C-2), and 177.0 (C-5); *m*/*z* 383 (M^+, 7%), 368 (8), 352 (8), 336 (14), 278 (100), 267 (7), 190 (12), 179 (9), 176 (15), 158 (9), 131 (14), 105 (46), and 73 (61).

3,4-*Dihydro*-4,5-*diphenyl*-4-*trimethylsilyloxy*-2H-*pyrrol*-2-*one* (**5b**). M.p. 102–104 °C (from hexane) (Found: C, 70.5; H, 6.7; N, 4.3. $C_{19}H_{21}NO_2Si$ requires C, 70.55; H, 6.54; N, 4.33%); ν_{max}(KBr) 1 750 (C=O), 1 585, and 1 545 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 0.10 (9 H, s, $SiMe_3$), 2.97 (2 H, dd, *J* 18 Hz, 3-H_2), 7.00–7.20 (8 H, m, ArH), and 7.77–7.93 (2 H, m, ArH); δ_C($CDCl_3$) 1.1 ($SiMe_3$), 49.8 (C-3), 85.0 (C-4), 190.6 (C-5), and 196.5 (C-2); *m*/*z* 308 (8%), 192 (100), 191 (58), 177 (41), 135 (10), 77 (10), 75 (22), and 73 (19).

(3R*,4R*)-3,4-*Dihydro*-3-*methyl*-4,5-*diphenyl*-4-*trimethylsilyloxy*-2H-*pyrrol*-2-*one* (**5c**) *and* (3R*, 4S*)-3,4-*dihydro*-4-*hydroxy*-3-*methyl*-4,5-*diphenyl*-2H-*pyrrol*-2-*one* (**5d**). Flash chromatography gave (in sequence) compounds (**5c**) and (**5d**).

Compound (**5c**): m.p. 111–112 °C (from hexane) (Found: C, 71.2; H, 6.9; N, 4.1. $C_{20}H_{23}NO_2Si$ requires C, 71.18; H, 6.87; N, 4.15%); ν_{max}(KBr) 1 755 (C=O), 1 585, and 1 550 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 0.10 (9 H, s, $SiMe_3$), 0.80 (3 H, d, *J* 7 Hz, 3-Me), 3.10 (1 H, q, *J* 7 Hz, 3-H), 7.10–7.30 (8 H, m, ArH), and 7.80–8.00 (2 H, m, ArH); δ_C($CDCl_3$) 1.0 ($SiMe_3$), 9.2 (3-Me), 51.7 (C-3), 88.8 (C-4), 191.7 (C-5), and 195.7 (C-2); *m*/*z* 337 (M^+, <1%). 322 (5), 206 (100), 205 (45), 191 (8), 177 (23), 115 (5), 75 (18), and 73 (27).

Compound (**5d**): m.p. ⩾180 °C (decomp.) (from EtOAc–hexane); ν_{max} 3 400 (OH), 1 750 (C=O), 1 585, and 1 550 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.30 (3 H, d, *J* 7 Hz, 3-Me), 2.75 (1 H, q, *J* 7 Hz, 3-H), 3.77 (1 H, s, 4-OH), 6.97–7.43 (8 H, m, ArH), and 7.90–8.06 (2 H, m, ArH); δ_C[$(CD_3)_2SO$] 9.0 (3-Me), 52.2 (C-3), 83.2 (C-4), and 195.0 and 195.1 (C-5 and C-2).

(2R*,4S*)-*Methyl* 2-(3,4-*dihydro*-2-*hydroxy*-4,5-*diphenyl*-4-*trimethylsilyloxy*-2H-*pyrrol*-2-*yl*)*acetate* (**8a**). Flash chromatography gave (in sequence) compounds (**5b**) (17%) and (**8a**).

Compound (**8a**): m.p. 156–158 °C (from EtOAc–hexane) (Found: C, 66.4; H, 6.8; N, 3.4. $C_{22}H_{27}NO_4Si$ requires C, 66.47; H, 6.85; N, 3.52%); ν_{max}(KBr) 3 180 (OH), 1 725 (C=O), and 1 615 cm^{-1} (C=N); δ_H(300 MHz; $CDCl_3$) (major isomer) 0.13 (9 H, s, $SiMe_3$), 2.46 and 2.67 (2 H, dd, *J* 14.6 Hz, CH_2), 2.58 and 2.63 (2 H, dd, *J* 15.2 Hz, CH_2), 3.61 (3 H, s, CO_2Me), 5.10 (1 H, br s, OH), and 7.0–7.8 (m, Ph); (minor isomer) 0.10 (9 H, s, $SiMe_3$), 2.57 (2 H, s, CH_2), 2.81 and 2.90 (2 H, dd, *J* 15.2 Hz, CH_2), 3.66 (3 H, s, CO_2Me), 5.07 (1 H, br s, OH), and 7.0–7.8 (m, Ph); δ_C($CDCl_3$) (major isomer) 1.4 ($SiMe_3$), 44.7 (CH_2), 51.7 (OMe), 54.6 (C-3), 90.4 (C-4), 97.2 (C-2), 171.8 (C-5), and 173.8 (C=O); (minor isomer) 1.7 ($SiMe_3$), 46.1 (CH_2), 51.7 (OMe), 54.1 (C-3), 91.1 (C-4), 97.6 (C-2), 171.7 (C-5), and 175.3 (C=O); *m*/*z* 382 (*M* − 15, 7%), 366 (*M* − 31, 6), 294 (33), 276 (100), 221 (22), 217 (32), 179 (26), 177 (9), 173 (10), 131 (15), 105 (26), 77 (12), 75 (22), and 73 (39).

1,5-*Dihydro*-4,5-*diphenyl*-5-*trimethylsilyloxy*-2H-*pyrrol*-2-*one* (**6a**) *and* (2R*,4S*)-*methyl* 2-(3,4-*dihydro*-2,4-*dihydroxy*-4,5-*diphenyl*-2H-*pyrrol*-2-*yl*)*acetate* (**8b**). Product purification by flash chromatography (hexane–EtOAc, 1:1) gave (in sequence) compounds (**6a**) and (**8b**).

Compound (**6a**): m.p. 145–147 °C (from aq. MeOH); ν_{max}(KBr) 3 240 (NH), and 1 705 and 1 675 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 0.13 (9 H, s, $SiMe_3$), 6.27 (2 H, s, 3-H and NH), and 6.97–7.40 (10 H, m, Ph); δ_C($CDCl_3$) 1.1 ($SiMe_3$), 91.0 (C-5), 119.0 (C-3), 162.4 (C-4), and 171.6 (C-2); *m*/*z* 323 (M^+, 100%), 308 (37), 294 (26), 246 (30), 234 (22), 192 (37), 177 (19), 131 (19), 105 (30), 102 (22), 77 (18), 75 (37), and 73 (33).

Compound (**8b**): m.p. 144–146 °C (decomp.) (from EtOAc–hexane) (Found: C, 69.8; H, 5.9; N, 4.0. $C_{19}H_{19}NO_4$ requires C, 70.14; H, 5.89; N, 4.30%); ν_{max}(KBr) 3 500 (OH), 3 120 (OH), 1 715 (C=O), and 1 620 cm^{-1} (C=N); δ_H(300 MHz; $CDCl_3$) 2.53–3.30 (4 H, 2dd, *J* 15, 15, 15, and 17 Hz, 2 × CH_2), 3.69 and 3.75 (3 H, 2 s, OMe), 4.09 and 4.61 (1 H, br s and br s, OH), and 7.20–7.85 (10 H, m, Ph); δ_C($CDCl_3$) 44.1 and 45.3 (CH_2), 51.7 and 51.9 (OMe), 55.5 and 55.9 (C-3), 88.1 and 89.1 (C-4), 97.5 and 98.3 (C-2), 171.3 and 172.4 (C-5), and 175.2 (C=O); *m*/*z* 325

(M^+, <3%), 294 (9), 252 (5), 222 (100), 204 (45), 190 (7), 172 (6), 162 (17), 149 (34), 144 (25), 131 (15), 120 (16), 116 (17), 105 (67), and 77 (25).

1,5-*Dihydro*-3-*methyl*-4,5-*diphenyl*-5-*trimethylsilyloxy*-2H-*pyrrol*-2-*one* (**6b**), 1,5-*dihydro*-5-*methoxy*-3-*methyl*-4,5-*diphenyl*-2H-*pyrrol*-2-*one* (**6c**), *and* 1,3-*dihydro*-3-*methoxy*-3-*methyl*-4,5-*diphenyl*-2H-*pyrrol*-2-*one* (**7**). Product purification by flash chromatography (hexane–EtOAc, 1:1) gave (in sequence) compounds (**6b**) and a mixture of isomers (**6c**) and (**7**) in a ratio ~4:6 (by ^{1}H NMR spectrometry). Analytically pure isomers (**6c**) and (**7**) were obtained by fractional recrystallization of the above mixture from ethyl acetate; compound (**7**) was the most insoluble.

Compound (**6b**): m.p. 134–136 °C (from EtOAc–hexane) (Found: C, 71.1; H, 6.7; N, 3.9. $C_{20}H_{23}NO_2Si$ requires C, 71.18; H, 6.87; N, 4.15%); ν_{max}(KBr) 3 170 (NH), 1 705 and 1 690 (C=O), 1 600, and 1 570 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 0.15 (9 H, s, $SiMe_3$), 2.00 (3 H, s, 3-Me), 6.40 (1 H, br s, NH), and 7.00–7.30 (10 H, m, Ph); δ_C($CDCl_3$) 1.2 ($SiMe_3$), 9.8 (3-Me), 90.3 (C-5), 155.4 (C-4), and 173.3 (C-2); *m/z* 337 (M^+, 100%), 322 (59), 308 (6), 260 (41), 248 (22), 192 (6), 145 (13), 116 (32), 115 (29), 105 (36), 77 (14), 75 (20), and 73 (41).

Compound (**7**): light yellow crystalline solid, m.p. ⩾ 195 °C (decomp.) (Found: C, 77.4; H, 6.0; N, 5.2. $C_{18}H_{17}NO_2$ requires C, 77.40; H, 6.13; N, 5.01%); ν_{max}(KBr) 3 190 (NH), 1 710 (C=O), and 1 600 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.40 (3 H, s, 3-Me), 3.40 (3 H, s, OMe), 7.20 and 7.30 (10 H, s and s, Ph), and 8.50 (1 H, br s, NH); δ_C($CDCl_3$) 21.7 (3-Me), 52.7 (OMe), 83.7 (C-3), and 179.8 (C-2); *m/z* 279 (M^+, 49%), 264 (16), 248 (100), 115 (7), 104 (11), and 77 (7).

Compound (**6c**): m.p. ⩾ 162 °C (decomp.) (Found: C,77.2; H, 6.1; N, 4.8%); ν_{max}(KBr) 3 240 (NH), 1 710, and 1 680 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 2.10 (3 H, s, 3-Me), 3.33 (3 H, s, OMe), 6.30 (1 H, br s, NH), and 7.20 (10 H, s, Ph); δ_C($CDCl_3$) 9.8 (3-Me), 49.6 (OMe), 93.1 (C-5), 151.5 (C-4), and 172.9 (C-2); *m/z* 279 (M^+, 97%), 264 (41), 248 (100), 176 (11), 170 (7), 163 (9), 145 (13), 116 (47), 104 (16), and 77 (16).

4-*Hydroxy*-5-*methoxy*-3,3-*dimethyl*-4,5-*diphenylpyrrolidin*-2-*one* (**18**).—A solution of the crude product (**3**) (4.8 mmol) in anhydrous methanol (25 ml) was refluxed for 14 h, after which it was concentrated and cooled to room temperature. Spontaneous crystallization occurred in the receiving flask. The white crystals were collected to yield the title compound (**18**) (1.18 g, 80% based on benzil) (only one diastereoisomer by ^{1}H NMR analysis), m.p. 165–167 °C; ν_{max}(KBr) 3 510 (OH) and 1 710 cm^{-1} (C=O); δ_H(300 MHz; $CDCl_3$) 0.82 (3 H, s, 3-Me), 1.57 (3 H, s, 3-Me), 3.15 (3 H, s, OMe), 4.32 (1 H, s, OH), 6.93–7.29 (10 H, m, Ph), and 8.67 (1 H, br s, NH); δ_C($CDCl_3$) 20.7 (3-Me), 24.4 (3-Me), 49.0 and 49.7 (OMe and C-3), 85.5 (C-4), 93.7 (C-5), and 184.0 (C-2).

3,4-*Dihydro*-4-*hydroxy*-3,3-*dimethyl*-4,5-*diphenyl*-2H-*pyrrol*-2-*one* (**5a**).—In a flask equipped with a Dean–Stark device for azeotropic distillation of methanol and a reflux condenser was placed a solution of the pyrrolidinone (**18**) (750 mg, 2.4 mmol) in anhydrous benzene (50 ml), and 10% Pd/C (75 mg) was added. Enough benzene was added to the Dean–Stark device to avoid loss of solvent from the reaction mixture. Reflux was maintained for 9 h, after which the catalyst was filtered off and the solvent was evaporated off to yield the *title compound* (**5a**) (670 mg, quantitative) as a white amorphous solid, m.p. 182–184 °C (from EtOAc) (Found: C, 77.2; H, 6.2; N, 4.9. $C_{18}H_{17}NO_2$ requires C, 77.40; H, 6.18; N 5.01%); ν_{max}(KBr) 3 240 (OH), 1 750 (C=O), 1 585, and 1 550 cm^{-1}; δ_H[60 MHz; $(CD_3)_2SO$] 0.57 (3 H, s, 3-Me), 1.23 (3 H, s, 3-Me), 6.77 (1 H, s, OH), 7.20–7.50 (8 H, m, ArH), and 7.97–8.13 (2 H, m, ArH); δ_C[$(CD_3)_2SO$] 20.3 (3-Me), 23.9 (3-Me), 52.0 (C-3), 87.9 (C-4), 194.5 (C-5), and 196.5 (C-2); *m/z* 279 (M^+, 5%), 264 (5), 251 (6), 148 (100), 133 (13), 104 (17), 103 (13), and 77 (12).

1,5-*Dihydro*-5-*hydroxy*-4,5-*diphenyl*-2H-*pyrrol*-2-*one* (**19a**).—A solution of compound (**6a**) (220 mg, 0.7 mmol) in anhydrous methanol (5 ml) was stirred at room temperature for 1 day. The solvent was evaporated off under reduced pressure to yield the *title compound* (**19a**) (170 mg, quantitative), which was recrystallized from aq. MeOH as a white crystalline solid, m.p. ⩾ 175 °C (decomp.) (Found: C, 76.5; H, 5.0; N, 5.3. $C_{16}H_{13}NO_2$ requires C, 76.48; H, 5.21; N, 5.57%); ν_{max}(KBr) 3 410 (OH), 3 180 (NH), and 1 685 cm^{-1} (C=O); δ_H(60 MHz; CD_3OD) 6.43 (1 H, s, 3-H) and 7.10–7.70 (10 H, m, Ph); δ_C (CD_3OD) 92.4 (C-5), 120.9 (C-3), 165.0 (C-4), and 174.9 (C-2); *m/z* 251 (M^+, 68%), 234 (7), 233 (5), 222 (11), 180 (29), 174 (10), 156 (10), 146 (10), 131 (34), 122 (22), 105 (100), 102 (62), 77 (40), and 51 (11).

1,5-*Dihydro*-5-*hydroxy*-3-*methyl*-4,5-*diphenyl*-2H-*pyrrol*-2-*one* (**19b**).—A solution of compound (**6b**) (140 mg, 0.4 mmol) in anhydrous methanol (3.5 ml) was stirred at room temperature for 1 day. The solvent was evaporated off under reduced pressure to yield the *title compound* (**19b**) (110 mg, quantitative), which was recrystallized from aq. MeOH as a white crystalline solid, m.p. ⩾ 180 °C (decomp.) (Found: C, 76.7; H, 5.5; N, 5.0. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28%); ν_{max}(KBr) 3 310 (OH), 3 180 (NH), and 1 680 cm^{-1} (C=O); δ_H(60 MHz; CD_3OD) 1.93 (3 H, s, 3-Me) and 7.07–7.47 (10 H, m, Ph); δ_C(CD_3OD) 9.7 (3-Me), 90.8 (C-5), 157.4 (C-4), and 175.4 (C-2); *m/z* 265 (M^+, 72%), 248 (12), 247 (15), 236 (8), 231 (23), 188 (20), 144 (20), 122 (22), 116 (100), 115 (65), 105 (57), 89 (9), 77 (28), and 51 (12).

Acknowledgements

We thank Professor J. Plumet (Universidad Complutense de Madrid) and Professor F. Gaviña (Universidad Valencia) for their interest to this work and for valuable suggestions, and Dra. P. Ballesteros (UNED) for performing the NOE and NOESY experiments. One of us (J. R.-L.) gratefully acknowledges the Dirección General de Polífica Científica (MEC, Spain) for doctoral fellowship. We acknowledge financial support by the DGICYT (Project PB87-0064-C03-00) (MEC, Spain).

References

1 B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, J. Plumet, and M. M. Sánchez, *Tetrahedron Lett.*, 1985, **26**, 4403.
2 B. Alcaide, R. Alajarín, J. Plumet, and J. Rodríguez-Lopez, *Synthesis*, 1988, 440.
3 B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, J. Plumet, and J. Rodríguez-Lopez, *Tetrahedron Lett.*, 1986, **27**, 5129.
4 B. Alcaide, A. Gómez, J. Plumet, and J. Rodríguez-López, *Tetrahedron*, 1989, **45**, 2751.
5 W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367 and references cited therein.
6 See among others: A. Warshawsky and D. Ben-Ishai, *J. Heterocycl. Chem.*, 1970, **7**, 917; W. L. F. Armarego and S. C. Sharma, *J. Chem. Soc. C*, 1970, 1600; H. D. Bartfeld and W. Flitsch, *Chem. Ber.*, 1973, **106**, 1423.
7 F. Gaviña, A. M. Costero, M. R. Andreu, M. Carda, and S. V. Luis, *J. Am. Chem. Soc.*, 1988, **110**, 4017.
8 For the synthesis of related azafulvenes, see: R. A. Jones and G. P. Bean, 'The Chemistry of Pyrroles,' Academic, London, 1977, pp. 425–428; C. F. Candy and R. A. Jones, *J. Chem. Soc. B*, 1971, 1405; T. Kobayashi, S. Kajigaeshi, and S. Kanemasa, *Heterocycles*, 1976, **4**, 1281; J. M. Muchowski and P. Hess, *Tetrahedron Lett.*, 1988, **29**, 777; B. L. Bray, P. Hess, J. M. Muchowski, and M. E. Scheller, *Helv. Chim. Acta*, 1988, **71**, 2053.
9 D. J. Hart, K. Kanai, D. G. Thomas, and T.-K. Yang, *J. Org. Chem.*,

1983, **48**, 289. For other synthesis of simple silylimines, see: J. C. Guillemin, L. Ammi, and J. M. Denis, *Tetrahedron Lett.*, 1988, **29**, 1287.
10 J. Weijlard, K. Pfister, E. F. Swanezy, C. A. Robinson, and M. Tishler, *J. Am Chem. Soc.*, 1951, **73**, 1216.
11 B. Alcaide, R. Fernández de la Pradilla, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, *J. Org. Chem.*, 1981, **46**, 3234; B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1649.
12 For related keto amide/ω-'carbinol' lactam tautomerism, see: R. E. Valters and W. Flitsch, 'Ring-Chain Tautomerism,' ed. A. R. Katritzky, Plenum, New York, 1985, p. 49.
13 P. C. Jocelyn and A. Queen, *J. Chem. Soc.*, 1957, 4437.
14 For a more recent synthesis of this and other related products, see: H. Roeber and K. Hartke, *Chem. Ber.*, 1975, **108**, 3262.
15 J. B. P. A. Wijnberg, H. E. Schoemaker, and W. N. Speckamp, *Tetrahedron*, 1978, **34**, 179.
16 For a closely related example, see: A. R. Butler and E. Leitch, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1972.

Paper 0/00634C
Received 12*th February* 1990
Accepted 26*th March* 1990