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Lewis-acid-induced reactions of α-methoxyglycinamide derivatives with silyl enol ethers. Formation of 3-amino-2-pyrrolidinones and 3-amino-2-pyrrolinones

Eric C. Roos[a], Henk Hiemstra*[,a], W. Nico Speckamp*[,a], Bernard Kaptein[b], Johan Kamphuis[b] and Hans E. Schoemaker[b]

[a] Department of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands
[b] DSM Research, Department of Bio-Organic Chemistry, P.O. Box 18, 6160 MD Geleen, The Netherlands
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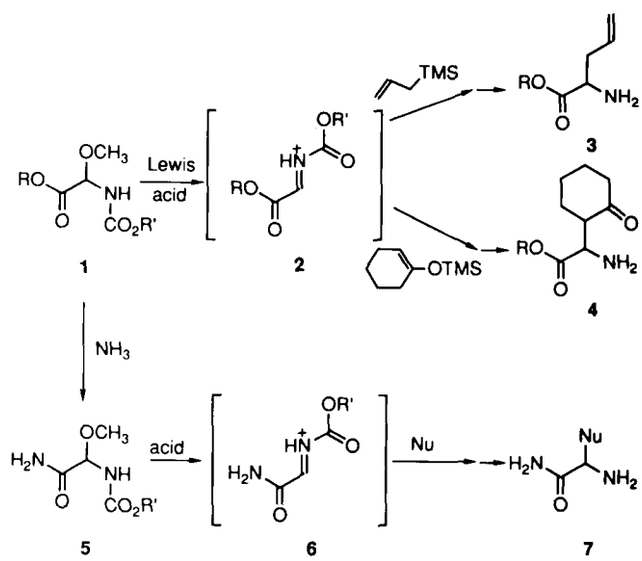
Abstract. In order to develop an expedient synthetic route to γ-oxo-α-aminocarboxamides, five different α-(alkoxycarbonyl)amino-α-methoxyacetamides were subjected to borontrifluoride-etherate-mediated reactions with one silyl ketene acetal and four silyl enol ethers. Reactions of primary and secondary amides did not lead to the desired C–C-bond formation. Reactions of the tertiary *N,N*-dimethylamide gave the expected γ-oxo-α-aminocarboxamides. The reaction of an *N*-methoxy--*N*-trimethylsilylcarboxamide with the ketene acetal also proceeded normally. However, the initial products of the latter amide with silyl enol ethers reacted further by cyclization, respectively, to give a cyclic *N*-methoxy-*N*-acyliminium intermediate. Depending on structural features of the enol ether used, this iminium intermediate suffered either proton loss and isomerization to give protected 3-amino-1- methoxy-Δ^3-pyrrolin-2-ones, or underwent a second coupling with the enol ether to give protected 3-amino-1-methoxypyrrolidin-2-ones.

Introduction

The synthesis of α-amino acids remains a topic of considerable interest because of the ever growing importance of both natural and unnatural amino acids[1]. It is crucial that such compounds are available in enantiomerically pure form due to the divergent biological activities of the enantiomers. Of the several methods known to obtain α-amino acids as pure enantiomers[2], a particularly attractive method involves the use of an L-specific aminopeptidase to perform enzymatic kinetic resolution of a racemic mixture of α-amino amides[3].

Recently, Lewis-acid-mediated reactions of α-methoxyglycine esters (**1**) with different types of π nucleophiles, in particular allylsilanes[4] and silyl enol ethers (Scheme 1)[5] have been investigated. These methods constitute versatile routes to racemic (protected) γ,δ-unsaturated α-amino acids (*e.g.*, **3**)[2] and γ-oxo-α-amino acids (*e.g.*, **4**)[5], respectively. An essential feature of this methodology is the intermediacy of iminium ion **2**, which is a highly electrophilic species due to the presence of carbonyl substituents on both carbon and nitrogen[6].

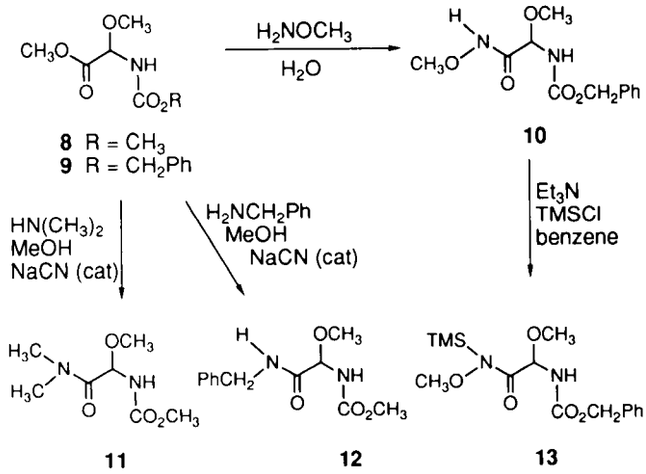
Continuing the work in this area, we have investigated the use of carboxamide **5** as the starting material for a similar acid-mediated coupling via **6**. In this way, rapid access would be gained to racemic α-amino amides **7**, which are the substrates required for the above-mentioned enzymatic approach to enantiomerically pure α-amino acids. Coupling of **6** with allylsilanes was successful, as will be reported elsewhere[7]. In this report, our study on the acid-mediated behaviour of primary amide **5**, as well as secondary and tertiary analogues, towards four silyl enol ethers and a silyl ketene acetal is described.



Scheme 1

Results and discussion

The conditions used for the successful conversion of **1** to **4** (boron trifluoride etherate, dichloromethane)[5] did not furnish products that could be isolated when applied to coupling of silyl enol ethers with primary amide **5**. One might argue that the initial products being primary γ-oxocarboxamides could cyclize to five-membered 5-hydroxylactams[6] and thus complicate the reaction course. However, we believe that a fast Lewis-acid-catalyzed silyl shift from the silyl-enol-ether oxygen to the amide nitrogen occurred before the intended reaction could take place. In fact, most of the nucleophile was recovered as cyclohexanone after attempted reaction with 1-(trimethylsiloxy)cyclohexene.

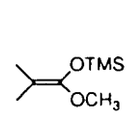
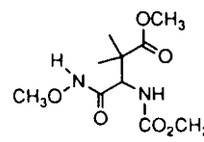
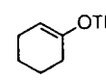
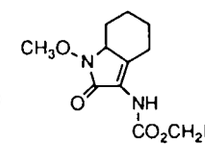
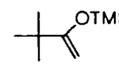
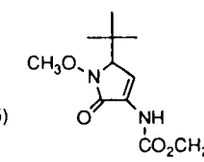
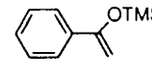
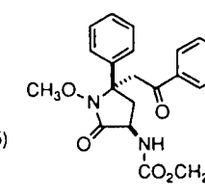
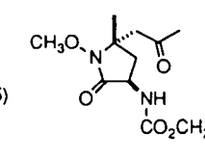
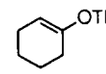
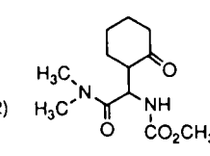
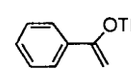
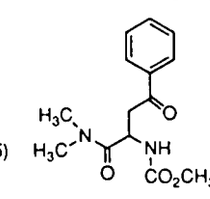


Scheme 2

Therefore, we turned our attention to secondary and tertiary amides in order to remedy this problem. This study was further prompted by the recent finding that certain secondary amides can be successfully applied in the enzymatic resolution process[7]. Starting from the readily available α-methoxyglycine esters **8** and **9**[8] (Scheme 2), the amides **10–12** were synthesized using straightforward aminolysis reactions[9]. While **10** was rapidly formed with aqueous *O*-methylhydroxylamine, the formation of **11** and **12** was efficiently catalyzed by a small amount of sodium cyanide[9b]. Secondary *N*-methoxycarboxamide **10** also failed to undergo the desired reaction with silyl enol ethers. However, after substitution of the remaining amide hydrogen through silylation[10], a useful starting material (**13**) was obtained. The identity of **13** was inferred from the ^{1}H NMR data. The carbamate NH signal of **10** (5.95 ppm, d, *J* 7.7 Hz) was still present in **13** (5.83 ppm, d, *J* 9.6 Hz), whereas the *N*-methoxyamide hydrogen of **10** (9.26 ppm, s) had disappeared in **13**[11]. Silylamide **13** was rather sensitive and was, therefore, used immediately without purification in the reaction with silyl enol ethers. In a typical experiment, 2 equiv of boron trifluoride etherate were added to a mixture of the glycinamide and the silicon nucleophile in dichloromethane at −78 °C. After stirring for 15 min at this temperature, the mixture was allowed to warm up to room temperature, and stirring was then continued for another 3 h.

Entries 1–5 in Table I show the results of reactions of **13** with silicon nucleophiles **14–18**. Only ketene acetal **14** gave the expected product, *i.e.*, ester **19** (with *N*-desilylation probably taking place during work-up). However, coupling of silyl enol ethers **15–18** gave rise to formation of γ-lactam

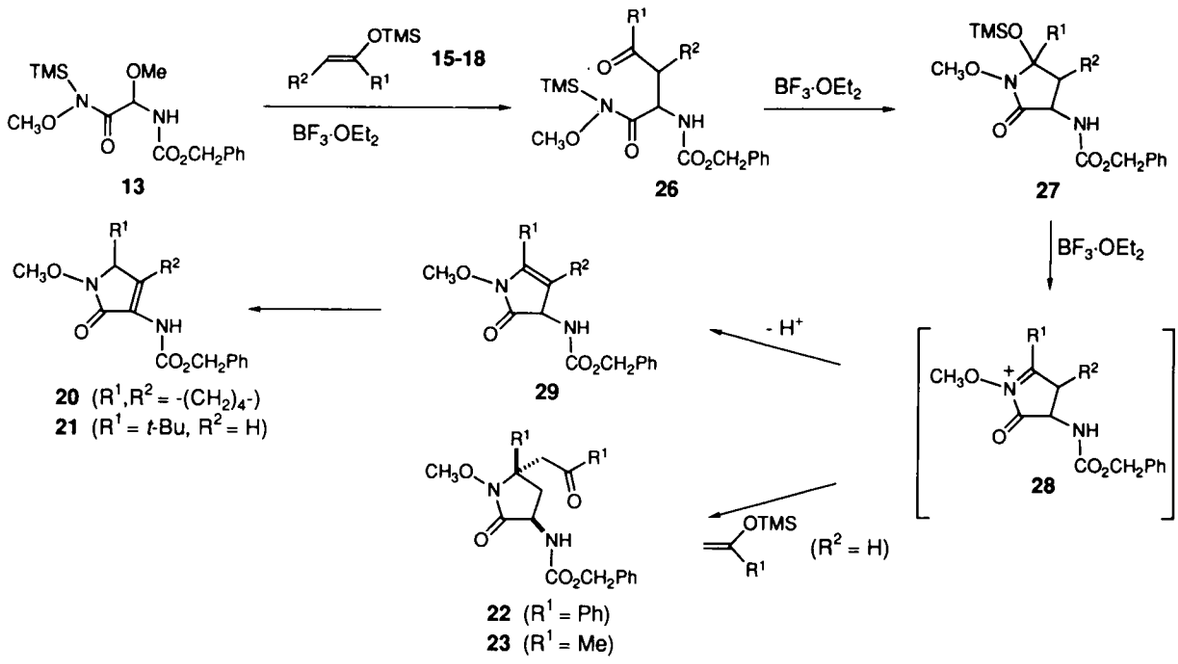
Table I **Coupling of α-methoxyglycinamide derivatives with silyl enol ethers and ketene acetal (14-18)**

Entry	Precursor[a]	Silicon nucleophile (equiv)		Product (yield)[b]
1	13		**14** (1.5)	 **19** (61%)
2	13		**15** (1.5)	 **20** (71%)
3	13		**16** (1.5)	 **21** (32%)
4	13		**17** (2.5)	 **22** (47%)
5	13		**18** (1.5)	 **23** (39%)
6	11		**15** (1.2)	 **24** (60%)
7	11		**17** (1.5)	 **25** (51%)

[a]For structures, see Scheme 2 [b]In entries 1-5, yields include the silylation step.

derivatives **20–23** as the only identifiable products. Interestingly, products **22** and **23** contained two equivalents of the nucleophile.

A mechanistic rationale for the formation of **20–23** is shown in Scheme 3. Under the influence of boron trifluoride etherate, the initial product **26** first cyclizes to **27**[12] and then ionizes to *N*-acyl-*N*-methoxyiminium ion **28**, the crucial intermediate. This species may lose a proton and further isomerize to produce **20** and **21**. Definitive structural proof for the location of the double bonds in these compounds was not readily obtained, although it was presumed that **20** and **21** are more stable than **29** in view of the additional conjugation between double bond and carbonyl. Moreover, the chemical shift of the vinylic proton in **21** (6.63 ppm, br s) is very similar to that of a comparable Δ^3-pyrrolinone, reported by *Katritzky* et al.[13]. If the double bond would be in



Scheme 3

the Δ^4 position as in **29**, the vinylic proton is expected to be found below 6 ppm[14,15]. In the presence of reactive and/or unhindered silyl enol ethers, species **28** may also give rise to a second C–C-bond formation to give **22** and **23**. These compounds were obtained as single isomers. The indicated stereochemistry was at first based on the notion that iminium species **28** should react at the least hindered face. This assumption was proved for compound **22** by using the NOE difference technique in ^{1}H NMR (see experimental). Unfortunately, the expected increases in the yields of **22** and **23** by using additional equivalents of silyl enol ether was not realized by experiment.

Tertiary amide **11** cleanly reacted with silyl enol ethers **15** and **17** (entries 6, 7; Table I) under the same conditions as in the case of **13** to give the normal coupling products **24** and **25** in reasonable yields. Compound **24** was obtained in a notably high isomer ratio of 9 : 1. The major isomer was obtained as a pure substance through recrystallization (m.p. 123–125°C). Neither mechanistic considerations[16] (apart from the probability of an acyclic transition state) nor NMR data allow a reliable assignment of the syn or anti stereochemistry to the major isomer, so that this must await X-ray determination.

Secondary amide **12** did not react in the desired fashion with silyl enol ethers (*cf.* **10**). We were also unable to effect a coupling reaction via silylation as carried out for **10** (Me_3SiCl, Et_3N, benzene; immediately followed by the coupling reaction). Apparently, the *N*-methoxy function in **10** renders the amide nitrogen atom more nucleophilic in the successful silylation of **10**, an example of the well-known alpha effect[17]. This alpha effect might also be responsible for the easy cyclization of intermediate **26** (Scheme 3).

In conclusion, we have shown that only the tertiary α-methoxyglycinamide **11** couples in a desired fashion with silyl enol ethers in the presence of boron trifluoride etherate to give the γ-oxo-α-aminocarboxamides **24** and **25** as products. The corresponding primary and secondary amides cannot be used in this process. In the case of secondary *N*-methoxyamide **10**, *N*-silylation is facile and the resulting tertiary amide **13** reacts well with silyl enol ethers. Depending on the nature of the silyl enol ether that is used, either 1 or 2 equivalents are consumed to produce *N*-methoxy-3-amino-2-pyrrolinones or the corresponding 2-pyrrolidinones, respectively[18]. The alpha effect in the *N*-methoxyamide is considered responsible for the ready silylation and cyclization.

Experimental

General information

Experimental techniques and analytical measurements were applied as previously described[4]. Mass spectra were recorded on a V.G. Micromass ZAB-HFqQ instrument. 1-Methoxy-2-methyl--1-(trimethylsiloxy)propene (**14**), 1-phenyl-1-(trimethylsiloxy)ethene (**17**) and 2-(trimethylsiloxy)propene (**18**) were purchased from Fluka.

2-(Benzyloxycarbonylamino)-2-methoxy-N-methoxyacetamide (**10**)

The α-methoxyglycine derivative methyl 2-methoxy-2-(benzyloxycarbonylamino)acetate **9**[8a] (30.0 g, 118.5 mmol) was dissolved in 30% aqueous *O*-methylhydroxylamine (360 ml). The solution was stirred at 50°C for 5 h. After removal of the volatiles *in vacuo*, the residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 25.9 g (96.6 mmol, 82%) of a white solid; m.p. 112–114°C. IR ($CHCl_3$): ν 3460–3360 (br, m, 2 × NH), 3000 (w), 2940 (w), 1760–1660 (br, s, 2 × C=O), 1495 (m). ^{1}H NMR (200 MHz): 9.26 (s, 1H, N*H*–OCH_3), 7.35 (s, 5H, Ph), 5.95 (d, 1H, *J* 7.7 Hz, N*H*), 5.29 (d, 1H, *J* 8.8 Hz, C*H*–N), 5.14 (s, 2H, O–CH_2–Ph), 3.77 (s, 3H, CH_3O–NH), 3.40 (s, 3H, CH_3O). ^{13}C NMR (50 MHz): 164.8 [*C*(O)–NHOCH$_3$], 156.2 [*C*(O)–N], 135.7 (Ph), 128.4, 128.2, 127.9 (Ph), 80.3 (*C*H–N), 67.2 (O–CH_2–Ph), 64.1 (CH_3O–N), 55.2 (CH_3O). An analytical sample was obtained by recrystallization from EtOAc/hexane. Anal. calcd. for $C_{12}H_{16}N_2O_5$ (268.27): C 53.73, H 6.01; found: C 53.79, H 6.08%.

2-Methoxy-2-(methoxycarbonylamino)-N,N-dimethylacetamide (**11**)

A solution of methyl 2-methoxy-2-(methoxycarbonylamino)acetate **8**[8b] (5.0 g, 28.2 mmol) in methanol (42.0 ml) was cooled to 0°C. Sodium cyanide (170 mg, 12 mol%) and dimethylamine (48.3 ml)[9b] were added (neat dimethylamine was cooled to –20°C and added as a liquid, using a precooled syringe). The mixture was allowed to warm up slowly to room temperature (in 1 h) and then poured out

into brine. The water layer was extracted with dichloromethane (3 ×). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo* to give 4.6 g (24.2 mmol, 86%) of a colorless oil, which solidified upon standing. IR ($CHCl_3$): ν 3455 (s, NH), 3000 (s), 2950 (s), 2910 (w), 1720 (br, s, C=O carbamate), 1645 (br, s, C=O amide), 1490 (s), 1075 (s), 1050 (s). ^{1}H NMR (200 MHz): 6.41 (d, 1H, *J* 8.8 Hz, N*H*), 5.43 (d, 1H, *J* 8.8 Hz, C*H*–N), 3.56 [s, 3H, $CH_3OC(O)$–N], 3.20 (s, 3H, CH_3O), 2.96 (s, 3H, CH_3–N), 2.84 (s, 3H, CH_3–N). ^{13}C NMR (50 MHz): 165.8 [*C*(O)–$N(CH_3)_2$], 156.5 [*C*(O)–N], 77.5 (*C*H–N), 53.6 and 52.0 (CH_3O, CH_3O), 36.3 and 35.4 (CH_3–N, CH_3–N). Accurate mass 190.0961 (calcd. for $C_7H_{14}N_2O_4$: 190.0954).

N-Benzyl-2-methoxy-2-(methoxycarbonylamino)acetamide (**12**)

A solution of methyl 2-methoxy-2-(methoxycarbonylamino)acetate **8**[8b] (1.0 g, 5.6 mmol) in methanol (2.0 ml) was cooled to 0°C. Sodium cyanide (30 mg, 12 mol%) and benzylamine (16.0 ml) were added. The mixture was allowed to warm up slowly to room temperature and then stirred at room temperature for 17 h. The mixture was poured into saturated aqueous NH_4Cl. The pH of this mixture was adjusted to 6 with aqueous HCl (2 N). The aqueous mixture was then extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (EtOAc/hexane, 1 : 1.5) to give 1.76 g (4.7 mmol, 84%) of a light yellow solid, m.p. 103.5–104.5°C. IR ($CHCl_3$): ν 3460–3400 (m, 2 × NH), 3020 (w), 2995 (m), 2950 (w), 2930 (w), 1725 (s, C=O carbamate), 1685 (s, C=O amide), 1505 (m), 1495 (s). ^{1}H NMR (200 MHz): 7.38–7.26 (m, 5H, Ph), 6.98 (br s, 1H, N*H*–CH_2Ph), 5.92 (d, 1H, *J* 7.4 Hz, N*H*), 5.28 (d, 1H, *J* 8.7 Hz, C*H*–N), 4.45 (m, 2H, CH_2Ph), 3.71 [s, 3H, $CH_3OC(O)$–N], 3.40 (s, 3H, CH_3O). ^{13}C NMR (50 MHz): 167.4 [*C*(O)–$NHCH_2$Ph], 157.1 [*C*(O)–N], 137.5 (Ph), 128.8, 127.8, 127.7 (Ph), 81.5 (*C*H–N), 55.4 and 52.5 (CH_3O, CH_3O), 43.6 (NH–CH_2Ph). An analytical sample was obtained by recrystallization from EtOAc/hexane. Anal. calcd. for $C_{12}H_{16}N_2O_4$ (252.27): C 57.13, H 6.40; found: C 57.19, H 6.36%.

General procedure for the coupling of **13** *with silicon nucleophiles*

A 0.2M solution of methoxyamide **10** in benzene was treated with triethylamine (2.2 equiv) and chlorotrimethylsilane (2.0 equiv), successively. The mixture was refluxed for 17 h, filtered under a blanket of dry nitrogen, and concentrated *in vacuo* to give silylamide **13**, as a colorless oil. ^{1}H NMR (200 MHz, C_6D_6): 7.15 (s, 5H, Ph), 5.83 (d, 1H, *J* 9.6 Hz, N*H*), 5.63 (d, 1H, *J* 9.6 Hz, C*H*–N), 5.03 (1/2 of AB system, 1H, *J* 14.1 Hz, O–CH_2–Ph), 4.97 (1/2 of AB system, 1H, *J* 14.1 Hz, O–CH_2–Ph), 3.48 (s, 3H, CH_3O–N), 3.26 (s, 3H, CH_3O), 0.18 [s, 9H, $Si(CH_3)_3$]. The silicon nucleophile (1.2–2.5 equiv) was added at room temperature to a 0.2M solution of silylamide **13** in dry dichloromethane. The reaction mixture was cooled to −78°C. Boron trifluoride etherate (1.5–2.5 equiv) was then added slowly to the reaction mixture. After a further 15 min at −78°C, the reaction mixture was allowed to warm up to room temperature and was then stirred for a further 3 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ and extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed.

2-(Benzyloxycarbonylamino)-N-methoxy-3-(methoxycarbonyl)-3-methylbutanamide (**19**)

According to the general procedure, starting from 705 mg (2.63 mmol) of **10**, 0.80 ml (688 mg, 3.95 mmol) of **14**, 13.0 ml of dichloromethane, and 0.65 ml (747 mg, 5.26 mmol) of boron trifluoride etherate, 543 mg (1.61 mmol, 61%) of **19** were obtained as a colorless oil, after flash chromatography, R_f 0.29 (EtOAc/hexane 1 : 1). IR ($CHCl_3$): ν 3430 (m, NH), 3390 (m, NH), 3020 (m), 3000 (s), 2950 (s), 2930 (s), 2850 (w), 1760–1640 (br, s, 3 × C=O), 1505–1490 (s). ^{1}H NMR (200 MHz): 9.66 (s, 1H, N*H*–OCH_3), 7.32 (s, 5H, C_6H_5), 6.39 (d, 1H, *J* 9.5 Hz, N*H*), 5.08 (s, 2H, O–CH_2–Ph), 4.21 (d, 1H, *J* 9.5 Hz, C*H*–N), 3.69 [s, 6H, CH_3O–NH, CH_3O–C(O)–C], 1.26 (s, 3H, CH_3–C), 1.22 (s, 3H, CH_3–C). ^{13}C NMR (50 MHz): 176.5 [CH_3–*C*(O)–C], 167.1 [*C*(O)–$NHOCH_3$], 156.5 [*C*(O)–N], 135.8 (Ph), 129.7, 128.4, 128.1, 127.8, 121.9 (C_6H_5), 67.2 (O–CH_2–Ph), 64.0 (CH_3O–NH), 58.2 (CH–N), 52.2 [CH_3O–C(O)–C], 44.1 [C(O)–*C*–CH], 22.4 (2 × CH_3–C). MS: M$^{+\bullet}$ – [CH_3–O–C(O)] = 279.

3-(Benzyloxycarbonylamino)-1,4,5,6,7,7a-hexahydro-1-methoxy-2H-indol-2-one (**20**)

According to the general procedure, starting from 712 mg (2.66 mmol) of **10**, 0.79 ml (678 mg, 3.98 mmol) of **15**[19], 13.0 ml of dichloromethane, and 0.65 ml (754 mg, 5.31 mmol) of boron trifluoride etherate, 599 mg (1.89 mmol, 71%) of **20** were obtained as a yellow oil, after flash chromatography, R_f 0.34 (EtOAc/hexane 1 : 1). IR ($CHCl_3$): ν 3440–3360 (br, m, NH), 3060 (w), 3030 (w), 3000 (s), 2940 (s), 2860 (m), 1760–1650 (br, s, 2 × C=O), 1540–1490 (s). ^{1}H NMR (200 MHz): 7.34 (s, 5H, Ph), 6.77 (s, 1H, N*H*), 5.12 (s, 2H, O–CH_2–Ph), 3.89–3.79 (m, 4H, C*H*–N, CH_3O–N), 3.16–3.09 (m, 1H, CH_2–C=C), 2.53–2.48 (m, 1H, CH_2–C=C), 2.40–1.20 [m, 8H, $CH(CH_2)_4$]. ^{13}C NMR (50 MHz): 165.3 [*C*(O)–$NOCH_3$], 153.3 [*C*(O)–N], 138.3, 135.7 (C=*C*–NH, C_6H_5), 128.4, 128.3, 128.1, 128.0, 127.9 (C_6H_5), 120.8 (*C*=C–NH), 67.3 (O–CH_2–Ph), 64.4 (CH_3O–N), 60.2 (*C*H–N), 32.4 (CH_2–C=C), 26.9, 26.0 (CH–CH_2–CH_2, =C–CH_2–CH_2), 22.6 (CH_2–CH_2–CH_2). Accurate mass 316.1416 (calcd. for $C_{17}H_{20}N_2O_4$ 316.1423).

3-(Benzyloxycarbonylamino)-5-tert-butyl-1,5-dihydro-1-methoxy-2H-pyrrol-2-one (**21**)

According to the general procedure, starting from 687 mg (2.56 mmol) of **10**, 662 mg (3.85 mmol) of **16**, 12.5 ml of dichloromethane, and 0.63 ml (728 mg, 5.13 mmol) of boron trifluoride etherate, 257 mg (0.81 mmol, 32%) of **21** were obtained as a crystalline compound, after flash chromatography, R_f 0.47 (EtOAc/hexane 1 : 2), m.p. 95–98°C. IR ($CHCl_3$): ν 3400 (m, NH), 3010 (w), 3000 (w), 2960 (m), 2930 (w), 2900 (w), 2860 (w), 1750–1660 (br, s, 2 × C=O), 1650 (m), 1520 (s). ^{1}H NMR (200 MHz): 7.37 (s, 5H, Ph), 7.08 (s, 1H, N*H*), 6.63 (br s, 1H, C=C*H*), 5.19 (s, 2H, O–CH_2–Ph), 3.99 (d, 1H, *J* 2.0 Hz, C*H*–N), 3.84 (s, 3H, CH_3O–N), 1.03 [s, 9H, $(CH_3)_3C$]. ^{13}C NMR (50 MHz): 165.0 [*C*(O)–$NOCH_3$], 153.1 [*C*(O)–N], 135.5, 129.2 (CH=*C*, Ph), 128.5, 128.4, 128.3, 128.1, 128.0 (Ph), 116.0 (*C*H=C), 68.2 (*C*H–N), 67.3 (O–CH_2–Ph), 62.2 (CH_3O–N), 34.5 [$(CH_3)_3C$], 26.5 [$(CH_3)_3C$]. An analytical sample was obtained by recrystallization from EtOAc/hexane. Anal. Calcd. for $C_{17}H_{22}N_2O_4$ (318.37): C 64.13, H 6.96; found: C 64.08, H 6.90%.

3-(Benzyloxycarbonylamino)-1-methoxy-5-(2-oxo-2-phenylethyl)-5-phenyl-2-pyrrolidinone (**22**)

According to the general procedure, starting from 403 mg (1.50 mmol) of **10**, 0.77 ml (723 mg, 3.76 mmol) of **17**, 8.0 ml of dichloromethane, and 0.46 ml (533 mg, 3.76 mmol) of boron trifluoride etherate, 326 mg (0.71 mmol, 47%) of **22** was obtained as a crystalline compound, after flash chromatography, R_f 0.35 (EtOAc/hexane 1 : 1), m.p. 59–62°C. IR ($CHCl_3$): ν 3480–3380 (br, m, NH), 3080 (w), 3060 (m), 3020 (m), 3000 (s), 2940 (m), 1760–1640 (br, s, 3 × C=O), 1505–1495 (br, s). ^{1}H NMR (200 MHz): 7.97 (d, 2H, *J* 7.7 Hz) and 7.63–7.26 (m, 13H, Ph), 5.59 (d, 1H, *J* 5.4 Hz, N*H*), 5.11 (s, 2H, O–CH_2–Ph), 4.51 (m, 1H, C*H*–N, irradiation gave a clear NOE effect on the doublet at 3.59 ppm and on the signal at 3.20 ppm), 4.06 [1/2 of AB system, 1H, *J* 17.8 Hz, CH_2–C(O)], 3.59 [1/2 of AB system, 1H, *J* 17.8 Hz, CH_2–C(O)], 3.55 (s, 3H, CH_3O–N), 3.20 (dd, 1H, *J* 9.8, 13.4 Hz, C–HC*H*–CH, *trans* to nitrogen), 2.51 (dd, 1H, *J* 8.2, 13.5 Hz, C–*CH*–CH, *cis* to nitrogen). ^{13}C NMR (50 MHz): 196.5 [C–*C*(O)–C], 168.1 [*C*(O)–$NOCH_3$], 156.0 [*C*(O)–N], 142.4, 136.8, 136.0 (Ph), 133.5, 128.7, 128.6, 128.4, 128.0, 127.9, 126.2 (Ph), 67.0 (O–CH_2–Ph), 64.2 (CH_3O–N), 63.9 (C_3C–N), 49.0 (*C*H–N), 41.7 [CH_2–C(O)], 38.4 (CH_2–CH). An analytical sample was obtained by recrystallization from EtOAc/hexane. Anal. calcd. for $C_{27}H_{26}N_2O_5$ (458.51): C 70.73, H 5.72; found: C 70.05, H 5.81%.

3-(Benzyloxycarbonylamino)-1-methoxy-5-(2-oxopropyl)-5-methyl-2-pyrrolidinone (**23**)

According to the general procedure, starting from 695 mg (2.59 mmol) of **10**, 0.93 ml (507 mg, 3.89 mmol, 70% solution) of

18, 13.0 ml of dichloromethane, and 0.63 ml (736 mg, 5.18 mmol) of boron trifluoride etherate, 334 mg (1.00 mmol, 39%) of **23** was obtained as a thick, yellow oil, after flash chromatography, R_f 0.23 (EtOAc/hexane 3 : 1). IR ($CHCl_3$): ν 3470–3380 (br, m, NH), 3000 (m), 2940 (m), 2890 (w), 1760–1660 (br, s, 3 × C=O), 1505 (s). ^{1}H NMR (200 MHz): 7.30 (s, 5H, Ph), 5.70 (d, 1H, *J* 6.6 Hz, N*H*), 5.05 (s, 2H, O–CH_2–Ph), 4.21 (m, 1H, C*H*–N), 3.86 (br s, 3H, CH_3O–N), 2.76–2.68 [m, 3H, C–CH_2–C(O), 1/2 of C–CH_2–CH], 2.09 [s, 3H, CH_3–C(O)], 1.83 (dd, 1H, *J* 9.0, 12.9 Hz, C–CH_2–CH), 1.43 (br s, 3H, CH_3–C). ^{1}H NMR (300 MHz, C_6D_6): 7.26–7.03 (m, 5H, Ph), 5.97 (d, 1H, *J* 6.6 Hz, N*H*), 5.08 (s, 2H, O–CH_2–Ph), 4.33 (m, 1H, C*H*–N), 3.68 (s, 3H, CH_3O–N), 2.51 (dd, 1H, *J* 9.9, 12.4 Hz, C–CH_2–CH), 2.10 [s, 2H, C–CH_2–C(O)], 1.68 (dd, 1H, *J* 9.2, 12.4 Hz, C–CH_2–CH), 1.58 [s, 3H, CH_3–C(O)], 1.20 (s, 3H, CH_3–C). ^{13}C NMR (50 MHz): 205.6 [C–*C*(O)–C], 167.3 [*C*(O)–$NOCH_3$], 155.9 [*C*(O)–N], 136.1 (Ph), 128.4, 128.0, 127.9 (Ph), 66.8 (O–CH_2–Ph), 64.6 (CH_3O–N), 60.0 (C_3C–N), 48.8 (*C*H–N), 48.5 [CH_2–C(O)], 37.0 (*C*H_2–C), 31.3 [CH_3–C(O)], 26.1 (*C*H_3–C). Accurate mass 334.1531 (calcd. for $C_{17}H_{22}N_2O_5$ 334.1529).

2-(Methoxycarbonylamino)-N,N-dimethyl-2-(2-oxocyclohexyl)acetamide (**24**)

In a similar fashion as the coupling of **13**, silyl enol ether **15** (0.62 ml, 551 mg, 3.24 mmol) was added at room temperature to a solution of dimethylamide **11** (512 mg, 2.70 mmol) in dichloromethane (13.0 ml). The reaction mixture was cooled to −78°C, and then boron trifluoride etherate (0.50 ml, 574 mg, 4.04 mmol) was added slowly to the reaction mixture. After a further 15 min at −78°C, the mixture was allowed to warm to room temperature and stirred for another 3 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ and extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed to give 410 mg (1.60 mmol, 60%) of **24**, as a white solid, R_f 0.31 (EtOAc/hexane 2.4 : 1), as a 9 : 1 mixture of isomers according to ^{1}H NMR. The major isomer could be obtained pure by recrystallization from EtOAc/hexane: m.p. 123–125°C. IR ($CHCl_3$): ν 3465 (m, NH), 3000 (m), 2970 (s), 2930 (m), 1740–1680 (br, s, 2 × C=O, ketone and carbamate), 1630 (s, C=O amide), 1505 (s). ^{1}H NMR (200 MHz, major isomer): 5.33 (d, 1H, *J* 10.4 Hz, N*H*), 4.82 (t, 1H, *J* 9.9 Hz, C*H*–N), 3.65 [s, 3H, CH_3O–C(O)–N], 3.25 (s, 3H, CH_3–N), 3.02–2.88 [m, 4H, CH_3–N, C*H*–C(O)], 2.36–1.37 [m, 8H, $(CH_2)_4$–C(O)]. ^{13}C NMR (50 MHz): 211.5 [CH_2–*C*(O)–CH], 171.8 [*C*(O)–N(CH_3)$_2$], 156.7 [*C*(O)–N], 52.9, 52.1, 49.9 [CH_3O–C(O), *C*H–N, CH_2–CH–C(O)], 41.9 [C(O)–CH_2–CH_2], 37.3 (*C*H_3–N), 35.6 (*C*H_3–N), 30.1 (CH–CH_2–CH_2), 27.7 (CH–CH_2–*C*H_2–CH_2), 24.8 [CH_2–*C*H_2–CH_2–C(O)]. An analytical sample was obtained by recrystallization from EtOAc/hexane. Anal. calcd. for $C_{12}H_{20}N_2O_4$ (256.30): C 56.24, H 7.86; found: C 56.21, H 7.93%.

2-(Methoxycarbonylamino)-N,N-dimethyl-4-oxo-4-phenylbutanamide (**25**)

According to the same procedure described for carbamate **24**, starting from 462 mg (2.43 mmol) of **11**, 0.75 ml (702 mg, 3.65 mmol) of **17**, 12.0 ml of dichloromethane, and 0.60 ml (690 mg, 4.86 mmol) of boron trifluoride etherate, 347 mg (1.25 mmol) of **25** was obtained as a crystalline compound, after flash chromatography, R_f 0.32 (EtOAc), m.p. 98.5–100.5°C. IR ($CHCl_3$): ν 3430 (w, NH), 3000 (m), 2950 (w), 1715 (s, C=O carbamate), 1675 (s, C=O ketone), 1635 (s, C=O amide), 1500 (s). ^{1}H NMR (200 MHz, $CDCl_3$): 7.89 (d, 2H, *J* 7.3 Hz) and 7.56–7.36 (m, 3H, Ph), 5.98 (d, 1H, *J* 9.2 Hz, N*H*), 5.24 (m, 1H, C*H*-N), 3.67–3.53 [m, 4H, CH_3O–C(O)–N, 1/2 of CH_2–C(O)], 3.33–3.24 [m, 4H, CH_3–N, 1/2 of CH_2–C(O)], 2.94 (s, 3H, CH_3–N). ^{1}H NMR (200 MHz, C_6D_6): 7.79 (d, 2H, *J* 7.3 Hz) and 7.15–6.90 (m, 3H, Ph), 5.51 (m, 1H, C*H*–N), 3.69 [dd, 1H, *J* 9.0, 17.4 Hz, CH_2–C(O)], 3.39 [s, 3H, CH_3O–C(O)–N], 3.05 [dd, 1H, *J* 9.0, 17.5 Hz, CH_2–C(O)], 2.94 (s, 3H, CH_3–N), 2.60 (s, 3H, CH_3–N). ^{13}C NMR (50 MHz): 197.4 [C–*C*(O)–C], 171.2 [*C*(O)–N(CH_3)$_2$], 156.2 [*C*(O)–N], 136.4 (Ph), 133.3, 128.5, 128.0 (Ph), 52.3 [CH_3O–C(O)], 47.2 (*C*H–N), 42.1 [CH_2–C(O)], 37.4 (*C*H_3–N), 35.9 (*C*H_3–N). An analytical sample was obtained by recrystallization from EtOAc/hexane. Anal. calcd. for $C_{14}H_{18}N_2O_4$ (278.31): C 60.42, H 6.52; found: C 60.40, H 6.58%.

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