

**1,3-DIPOLAR CYCLOADDITIONS OF NEW MESOIONIC COMPOUNDS.
SYNTHESIS OF 1*H*-PYRROLO[1,2-*c*]THIAZOLES, PYRROLIZINES
AND 5,6,7,8-TETRAHYDROINDOLIZINES**

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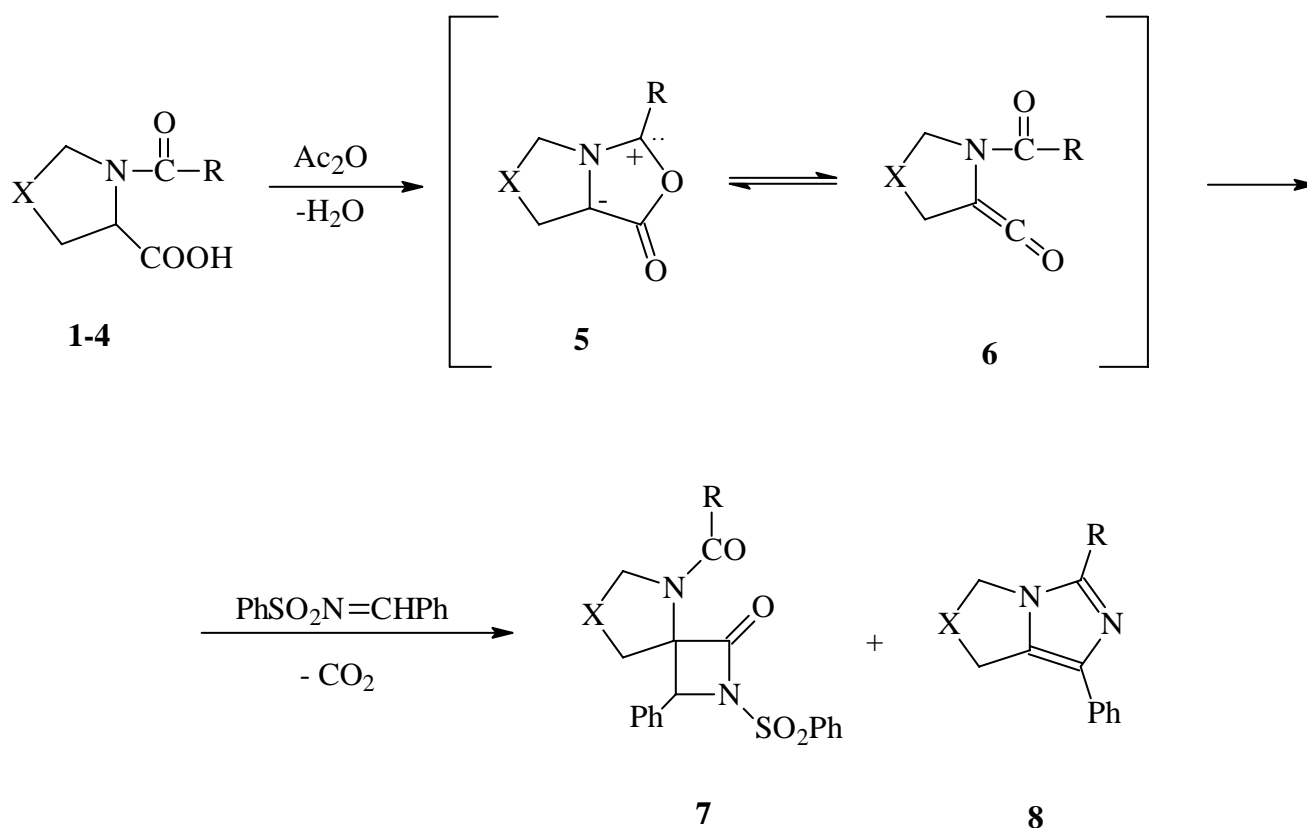
Abstract - We studied the 1,3-dipolar cycloaddition reactions between alkyne dipolarophiles and the new mesoionic compounds 2*H*,5*H*,7*H*-thiazolo[4,3-*b*]oxazol-2-one (**12**), 2*H*,5*H*,7*H*-pyrrolo[2,1-*b*]oxazol-2-one (**13**) and 2*H*,5*H*,7*H*-oxazolo[3,2-*a*]pyridin-2-one (**14**). These 1,3-dipoles were prepared *in situ* by means of cyclodehydration with acetic anhydride of the corresponding α -substituted 4-oxo-3-thiazolidine- (**9**), 2-oxo-1-pyrrolidine- (**10**) and 2-oxo-1-piperidineacetic acids (**11**). The cycloaddition reactions with alkyne dipolarophiles afforded single 1*H*-pyrrolo[1,2-*c*]thiazole, pyrrolizine and 5,6,7,8-tetrahydroindolizine derivatives, or a mixture of the two possible regioisomers, depending on whether symmetrical or unsymmetrical alkynes.

Introduction

We have previously reported the reactivity of the bicyclic mesoionic compounds (**5**) deriving from the cyclodehydration of cyclic *N*-acyl- α -amino acids as: *N*-acyl-(*R*)-thiazolidine-4-carboxylic acids (**1**), *N*-acyl-(*L*)-prolines (**2**), *N*-acyl-(*D,L*)-pipecolinic acids (**3**) and *N*-benzoyl-(*S*)-oxazolidine-4-carboxylic acid (**4**).^{1,2} The reaction with *N*-phenylmethylenbenzenesulfonamide afforded mixtures of diastereoisomeric spirocyclic β -lactams (**7**) and/or imidazo-condensed products (**8**) depending on the experimental conditions and the nature of the R and X groups (Scheme 1).

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Scheme 1

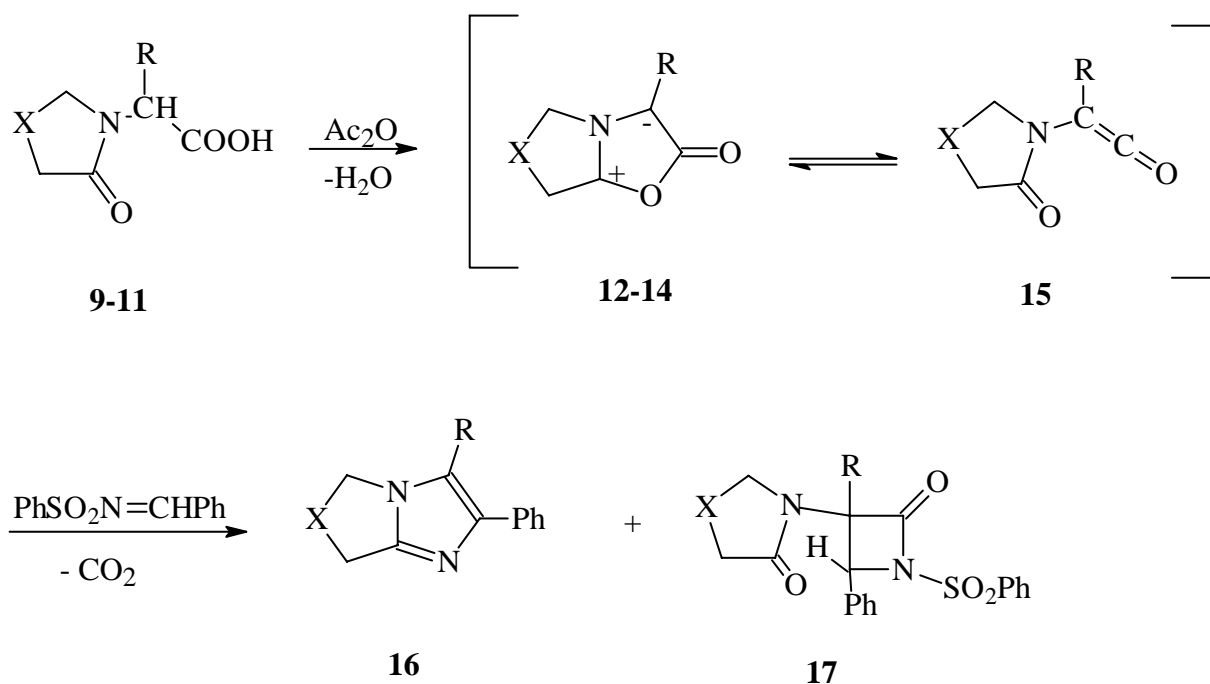


- 1** X = S, **a** R = Me, **b** R = Ph
2 X = CH_2 , **a** R = Me, **b** R = Ph
3 X = $(\text{CH}_2)_2$, **a** R = Me, **b** R = Ph
4 X = O, R = Ph

The cyclodehydration of these *N*-acyl- α -amino acids leads to the *in situ* formation of the bicyclic mesoionic compounds (**5**) and their ketene valence tautomers (**6**), which are respectively responsible for the formation of the products (**7**) and (**8**). The 1,3-dipolar cycloaddition reaction was completely regioselective, with only regioisomers (**8**) being obtained.

In connection with these results, we decided to study the reactivity of the mesoionic compounds (**12-14**) (Scheme 2), which have an opposite 1,3-dipolar reactive form from that of **5**, with the aim of obtaining the regioisomeric imidazo-condensed cycloadducts (**16**) on reaction with *N*-phenylmethylenesulfonamide. A survey of the literature showed that the α -amino acids (**9-11**), (the precursors of new dipoles (**12-14**)), have received little attention in regard to their synthesis, and that the 1,3-dipoles (**12-14**) had never been used before. To the best of our knowledge, few examples of analogous 1,3-dipoles were known,^{3,4} all of which had more complex structures, and no a systematic study had been made of their reactivity. We therefore decided to verify the reactivity of dipoles (**12-14**) with alkynes, generally the most reactive dipolarophiles.

Scheme 2



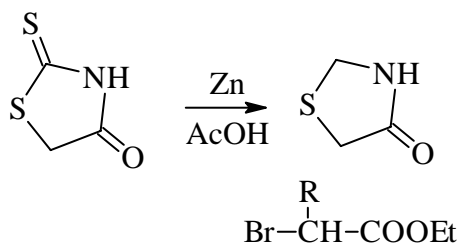
9,12	$\text{X} = \text{S},$	a	$\text{R} = \text{H},$	b	$\text{R} = \text{Me},$	c	$\text{R} = \text{Ph}$
10,13	$\text{X} = \text{CH}_2,$	a	$\text{R} = \text{H},$	b	$\text{R} = \text{Me},$	c	$\text{R} = \text{Ph}$
11,14	$\text{X} = (\text{CH}_2)_2,$	a	$\text{R} = \text{H},$	b	$\text{R} = \text{Me},$	c	$\text{R} = \text{Ph}$

Results and Discussion

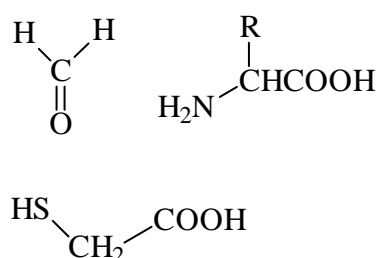
The synthesis of the α -substituted 4-oxo-3-thiazolidineacetic acids (**9a-c**) could follow the different routes shown in Scheme 3. Using route A, products (**9**) can be obtained by alkylation of the 4-oxo-thiazolidine with α -substituted α -bromoacetates in the presence of a base, followed by hydrolysis; route B can lead to the generation of the 4-oxothiazolidine ring by means of the condensation of an aldehyde (in our case formaldehyde), a mercaptoacetic acid and a primary amine (in our case an α -amino acid). The only report regarding compounds (**9**) is a patent showing the synthesis of **9a** and **9b** by route A.⁵ Route B is reported as having been used for the first time with α -amino acids, the fact that only aromatic aldehydes were used means that 2-aryl-substituted 4-oxothiazolidines were obtained.⁶ We tested both routes. In the first case, it was necessary to prepare the unavailable 4-oxothiazolidine. 4-Oxothiazolidines have been extensively studied and numerous syntheses have been reported, including the reduction of the inexpensive rhodanine with zinc dust in boiling acetic acid,⁷ which led to 4-oxo-thiazolidine in 58 % yield.

Scheme 3

Route A



Route B



9a R = H
9b R = Me
9c R = Ph

This was then alkylated with α -substituted α -bromoacetates in boiling THF with NaH as base. The final hydrolysis furnished products (**9a-c**) in 24%, 25% and 27% total yields from rhodanine.

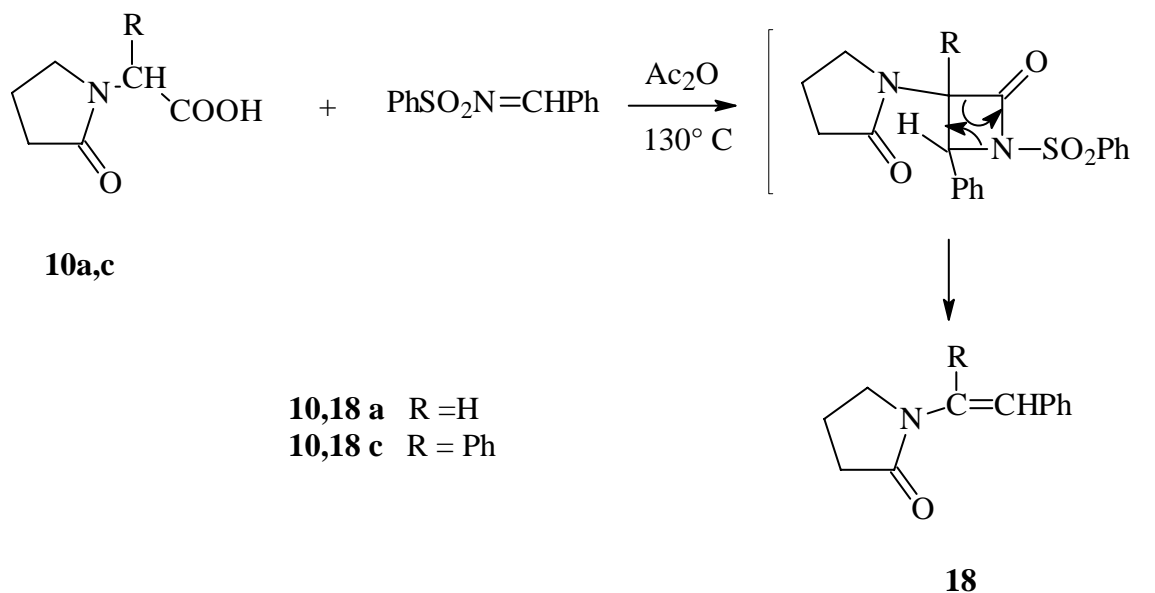
Following route B, products (**9a-c**) were synthesised by heating a mixture of polyoxymethylene, thioglycolic acid and the appropriate α -amino acid (in a ratio of 2:3:1) in boiling benzene and removing the water as it formed. In this way, products (**9a-c**) were obtained in 63%, 70% and 73% yields respectively.⁸ Route B therefore proved to be better.

The 2-oxo-1-pyrrolidineacetic acid and 2-oxo-1-piperidineacetic acid derivatives (**10a-c**) and (**11a-c**) were synthesised by alkylating 2-pyrrolidinone and 2-piperidinone with α -substituted α -bromoacetic acids in toluene in the presence of NaH. Compounds (**10a-c**) and (**11a-b**) were known,⁹⁻¹³ although some had not been completely described; the unknown **11c** was characterised.

Mesoionic compounds (**12-14**) were prepared *in situ* from the corresponding compounds (**9-11**). The use of acetic anhydride as a dehydrating agent and solvent allowed the cycloaddition reaction to be carried out at the suitable temperature of $T=120-130^\circ\text{C}$. The mesoionic intermediates (**12-14**) were less reactive than the reversed intermediates (**5**); possibly because it was more difficult for the oxygen of the lactam carbonyl residue to attack the carbon atom of the carboxylic group, and thus give the bicyclic 1,3-dipole.³

The reaction of **10a-c** with the *N*-phenylmethylenbenzenesulfonamide did not afford products (**16**) or (**17**) as expected (Scheme 2) but only small amounts (10-25%) of products (**18**), probably deriving from the unstable intermediate β -lactams as a result of a cycloreversion process (Scheme 4).

Scheme 4

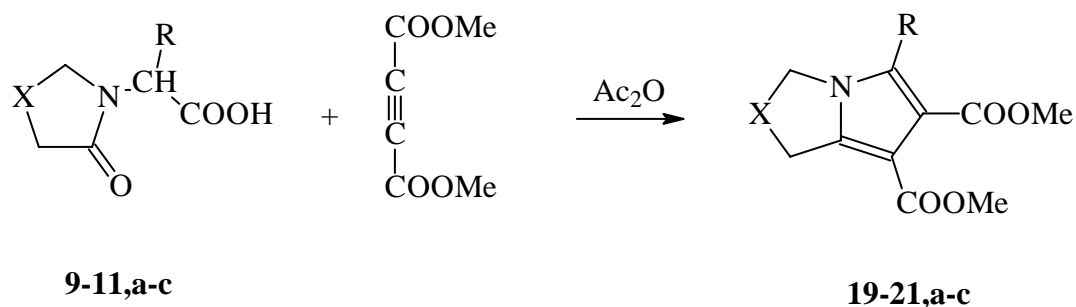


The possibility that **18** was formed by a 1,3-cycloaddition reaction between the dipole and the benzaldehyde deriving from a partial hydrolysis of the imine was rejected because there was no reaction of **10a** with an equimolar quantity of benzaldehyde. This result did not allow comparison of the regioselectivity of mesoionic compounds (**12-14**) with that of the reversed **5**. Moreover, the lower reactivity observed convinced us to use more reactive dipolarophiles as alkynes.

The first alkyne used was the dimethyl acetylenedicarboxylate: as shown in Table 1, all of the substrates (**9-11,a-c**) afforded the products (**19-21,a-c**) (Scheme 5) with yields ranging from 10% to 91%.

The yields were better when R was a methyl or phenyl group, and when X was one or two methylene groups instead of an heteroatom. This behavior is analogous with that observed with mesoionics (**5**).^{1,2}

Scheme 5



9,19	X = S	a R = H	b R = Me	c R = Ph
10,20	X = CH ₂	a R = H	b R = Me	c R = Ph
11,21	X = (CH ₂) ₂	a R = H	b R = Me	c R = Ph

Table 1

N°	X	R	Yield (%)
19a	S	H	10
19b	S	Me	28
19c	S	Ph	65
20a	CH ₂	H	21
20b	CH ₂	Me	76
20c	CH ₂	Ph	80
21a	(CH ₂) ₂	H	24
21b	(CH ₂) ₂	Me	34
21c	(CH ₂) ₂	Ph	91

The second alkyne used was the ethyl propiolate: the 1,3-dipoles (**12-14,a**) (R=H) did not react with this less reactive dipolarophile. The others gave mixtures of the regioisomeric products (**22-24b-c**) and (**25-27,b-c**) (Scheme 6) with total yields of between 10% and 92% (Table 2) and a ratio ranging from 55/45 to 87/13, as determined by the relative integration of the H-7 and H-6 signals present in the ¹H-NMR spectra of the crude reaction mixture.

The regiochemistry was assigned to the unknown products by comparing the chemical shift values in their ¹H-NMR spectra with those of the known products. Furthermore, a positive NOE effect was observed in the minor regioisomer obtained from the reaction of **10c** with ethyl propiolate, between the singlet at δ 6.8 relating to H-6, and a doublet at δ 7.48 relating to the ortho-protons of the C-5 phenyl group, thus allowing us to assign it structure (**26c**).

Scheme 6

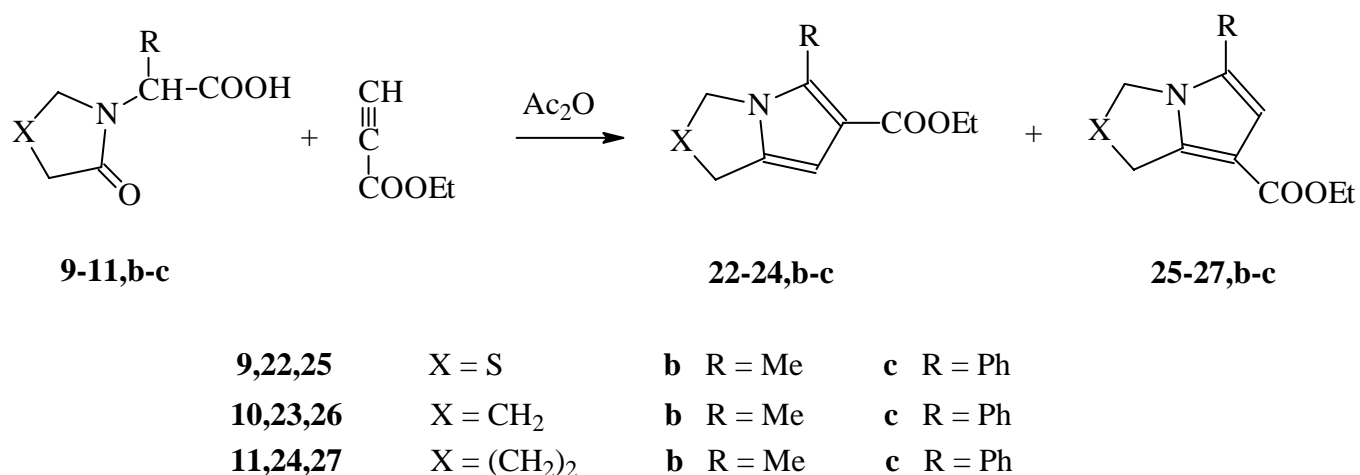


Table 2

N°	X	R	Yield (%) 22-24 + 25-27	Ratio 22-24 / 25-27
22b – 25b	S	Me	10	68 / 32
22c – 25c	S	Ph	73	87 / 13
23b – 26b	CH ₂	Me	49	60 / 40
23c – 26c	CH ₂	Ph	83	70 / 30
24b - 27b	(CH ₂) ₂	Me	28	69 / 31
24c – 27c	(CH ₂) ₂	Ph	92	55 / 45

As shown in Table 2, the main regioisomer is always that with the R and carbethoxy groups adjacent to, and deriving from the bond formation between the 1,3-dipole C-2 center and the propiolate dipolarophile β -carbon. The observed regioselectivity agrees with that reported for the reactions of analogous but reversed 1,3-dipoles (**5**) with alkyl propiolate,^{14,15} as the ratio between the two regioisomers in our mixtures was the opposite of those reported. In our case, regiocontrol seems to be rationalised by the FMO theory¹⁵ instead of a tether-based prediction¹⁶ that would lead to preferential bond formation between the C-2 tethered centre and the α -carbon of the propiolate.

Finally, substrates (**9c**, **10c** and **11c**) were reacted with another unsymmetrical dipolarophile, the 1,3-diphenylpropynone (Scheme 7 and Table 3). The lower yields of these cycloaddition reactions show the poor reactivity of this alkyne. Also in this case, mixtures of the new regioisomeric compounds (**28-30**) and (**31-33**) were obtained with a ratio always in favour of regioisomers (**28-30**). The regiochemistry of the products was assigned on the basis of the NOE results obtained from the couple deriving from the reaction between **10c** and the 1,3-diphenylpropynone.

Scheme 7

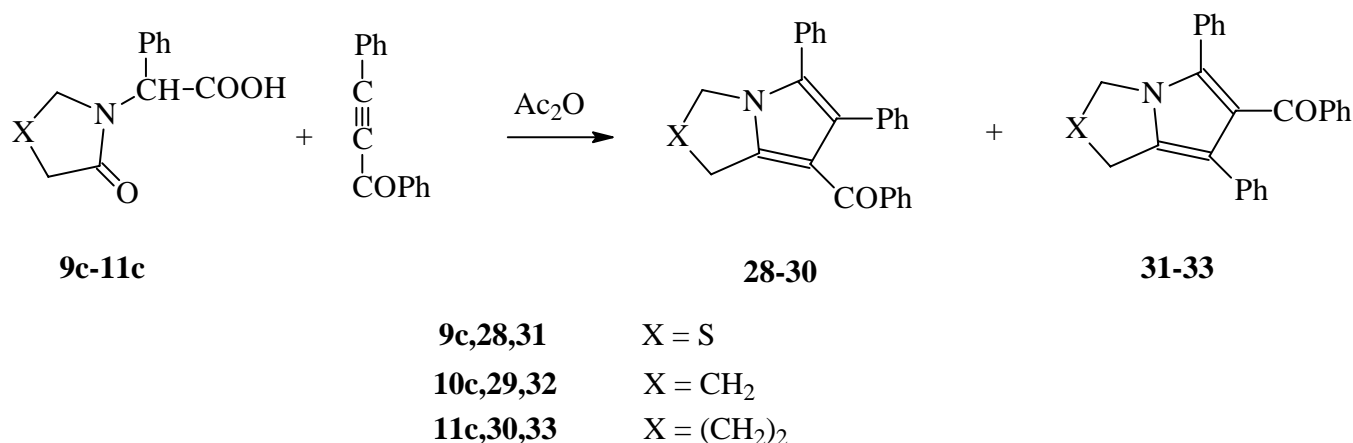


Table 3

N°	X	R	Yield (%) 28-30 + 31-33	Ratio 28-30 / 31-33
28 - 31	S	Ph	16	75 / 25
29 – 32	CH ₂	Ph	21	72 / 28
30 - 33	(CH ₂) ₂	Ph	95	90 / 10

The major regioisomer showed a positive NOE effect between the triplet at δ 2.89 relating to H-7, and the doublet at δ 7.55 relating to the H-ortho of the benzoyl group, thus indicating that the two groups of protons are close to each other as in structure (29). The other regioisomer showed a positive NOE effect between the triplet at δ 3.02 relating to H-7, and a doublet at δ 7.21 relating to the H-ortho of the C-1 phenyl, thus confirming structure (32). The observed regioselectivity agrees with the reported results of 1,3-cycloaddition reactions between the same 1,3-diphenylpropynone and various 1,3-dipoles (nitrile oxides and nitrile imides,¹⁷ mesoionic compounds such as the 3-methylsydnone¹⁸ and bis(1,3-dithiolylum-4-olates)¹⁹), and can be rationalized using the FMO theory.¹⁹

In conclusion, this is the first study of the reactivity of the bicyclic mesoionic compounds 2*H*,5*H*,7*H*-thiazolo[4,3-*b*]oxazol-2-one (12), 2*H*,5*H*,7*H*-pyrrolo[2,1-*b*]oxazol-2-one (13) and 2*H*,5*H*,7*H*-oxazolo[3,2-*a*]pyridin-2-one (14) towards alkyne dipolarophiles. The compounds were less reactive than the inverse 1,3-dipoles probably due to greater difficulty in ring closure. However, the reactions did allow us to obtain some new 1*H*-pyrrolo[1,2-*c*]thiazoles, pyrrolizine and 5,6,7,8-tetrahydroindolizine derivatives.

EXPERIMENTAL

General Methods: Melting points were measured using a Büchi apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded by means of a Bruker AC 300 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS; CDCl₃ was used as solvent if not otherwise stated. All coupling constants (*J*) are in Hertz. MS spectra were determined on a VG Analytical 7070 EQ mass spectrometer with a VG analytical 11/250 data system attached. IR spectroscopy was performed on a Perkin-Elmer 1725X FT-IR spectrometer. **4-Oxothiazolidine** was prepared with the reported method⁷ in 58% yield.

Preparation of 4-Oxo-3-thiazolidineacetic acids (9a-c).

Route A. A solution of 4-oxothiazolidine (0.5 g, 4.8 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (50% in oil, 0.23 g, 4.8 mmol) in THF (20 mL). The mixture was stirred and heated at

65° C for 1 h, then a solution of the α -substituted ethyl α -bromoacetate (4.8 mmol) in THF (5 mL) was added dropwise and the heating continued for 10-13 h. After evaporation of the solvent, the residue was taken up in CH₂Cl₂ (30 mL) and the solution was washed with water. The organic phase was dried (Na₂SO₄) and the solvent evaporated off. The residue was treated with MeOH (20 mL) and 1N NaOH (7.2 mL, 7.2 mmol) at rt for 4 h. After evaporation of the solvent the aqueous solution was extracted with AcOEt (2x10 mL), acidified with 10% HCl and extracted with AcOEt (3x15 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated. The products were recrystallized and identified by means of analytical and spectroscopic data. Products (**9a**, **9b**, **9c**) were obtained with 41, 43 and 47% yields respectively.

Route B. A mixture of thioglycolic acid (11.7 mL, 168 mmol), polyoxymethylene (3.35 g, 112 mmol of formaldehyde), α -amino acid (56 mmol) in benzene (100 mL) was heated at reflux temperature for 6 h removing the water as it was formed. After evaporation of the solvent the residue was treated with 10% HCl (80 mL) and extracted with AcOEt (4x50 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated. The unreacted thioglycolic acid was distilled off (T = 185°C, P = 15 mm Hg) and the residue was purified by column chromatography over silica gel (toluene/AcOEt = 25/75). Products (**9a**, **9b**, **9c**) were obtained with 63, 70 and 73% yields respectively.

4-Oxo-3-thiazolidineacetic acid (9a):⁵ colorless solid, mp 176-178 °C (EtOH); ¹H-NMR (CD₃COCD₃): δ 2.8 (br, 1H, COOH exchangeable), 3.5 (s, 2H, H-5), 4.15 (s, 2H, N-CH₂-CO), 4.55 (s, 2H, H-2). IR (nujol): ν 1711.92 cm⁻¹ (C-COO-), 1635.81 cm⁻¹ (N-CO-). MS (70eV, EI): m/e 161 [M⁺], 102, 88. Anal. Calcd for C₅H₇NO₃S: C, 37.27; H, 4.35; N, 8.69. Found: C, 36.98; H, 4.22; N, 8.55.

α -Methyl-4-oxo-3-thiazolidineacetic acid (9b):⁵ colorless solid, mp 70-72 °C (iPr₂O/iPrOH). ¹H-NMR: δ 1.45 (d, J=7.53, 3H, CH₃), 3.55, 3.6 (AB syst. J=15.7, 2H, H-5), 4.35, 4.5 (AB syst. J=7.18, 2H, H-2), 4.85 (q, J=7.53, 1H, N-CH-CO), 6.25 (br, 1H, COOH). IR (nujol): ν 1732.77 cm⁻¹ (C-COO-), 1642.47 cm⁻¹ (N-CO-). MS (70eV, EI): m/z 175 [M⁺], 138, 102. Anal. Calcd for C₆H₉NO₃S: C, 41.14; H, 5.14; N, 8.0. Found: C, 40.98; H, 5.36; N 8.15.

α -Phenyl-4-oxo-3-thiazolidineacetic acid (9c): colorless solid, mp 120-122 °C (iPr₂O/iPrOH). ¹H-NMR: δ 3.55, 3.6 (AB syst. J=15.82, 2H, H-5), 3.8, 4.65 (AB syst. J=8.68, 2H, H-2), 5.85 (broad, 1H, COOH), 6.0 (s, 1H, N-CH-CO), 7.25-7.45 (m, 5H, Ph). IR (nujol): ν 1738.58 cm⁻¹ (C-COO-), 1631.03 cm⁻¹ (N-CO-). MS (70eV, EI): m/z 237 [M⁺], 219, 192, 164, 118. Anal. Calcd for C₁₁H₁₁NO₃S: C, 55.69; H, 4.64; N, 5.90. Found: C, 55.56; H, 4.59; N 5.91.

Preparation of 2-Oxo-1-pyrrolidineacetic acids (10a-c) and 2-oxo-1-piperidineacetic acids (11a-c)

General method: A solution of 2-pyrrolidinone or 2-piperidinone (60 mmol) in toluene (15 mL) was added dropwise to a suspension of NaH (50% in oil, 6.34 g, 132 mmol) in toluene (80 mL). The mixture was stirred and heated at 60° C for 1 h, then a solution of the α -substituted α -bromoacetic acid (60 mmol) in toluene (10 mL) was added dropwise and the heating continued for 2-6 h. After evaporation of the solvent the residue was treated with water, acidified with conc. HCl (pH 2), and extracted with AcOEt (4x50 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated. The products were recrystallized and characterized by means of analytical and spectroscopic data.

2-Oxo-1-pyrrolidineacetic acid (10a): Yield 72%; mp 143 °C (lit.,⁹ 143 °C). ¹H-NMR: δ 2.1 (m, 2H, H-4), 2.45 (t, J=7.54, 2H, H-3), 3.5 (t, J=6.98, 2H, H-5), 4.05 (s, 2H, N-CH₂-CO), 4.6 (br, 1H, COOH).

α -Methyl-2-oxo-1-pyrrolidineacetic acid (10b): Yield 50%; mp 128 °C (lit.,¹⁰ 129 °C). ¹H-NMR: δ 1.45 (d, J=7.59, 3H, CH₃), 2.1 (m, 2H, H-4), 2.5 (t, J=7.62, 2H, H-3), 3.5 (m, 2H, H-5), 4.85 (q, J=7.59, 1H, N-CH-CO), 5.9 (br, 1H, COOH).

α -Phenyl-2-oxo-1-pyrrolidineacetic acid (10c): Yield 48%; mp 124 °C (lit.,¹¹ 125 °C).

2-Oxo-1-piperidineacetic acid (11a): Yield 53%; mp 180 °C (lit.,¹² 184 °C).

α -Methyl-2-oxo-1-piperidineacetic acid (11b): Yield 52%; mp 147 °C (lit.,¹³ 148 °C). ¹H-NMR: δ 1.45 (d, J=7.36, 3H, CH₃), 1.7 (m, 4H, H-4 and H-5), 2.45 (t, J=5.9, 2H, H-3), 3.25 (t, J=5.8, 2H, H-6), 4.95 (q, J=7.33, 1H, N-CH-CO), 7.3 (br, 1H, COOH).

α -Phenyl-2-oxo-1-piperidineacetic acid (11c): Yield 74%; mp 148-149 °C (iPrOH). ¹H-NMR: δ 1.75 (m, 4H, H-4 and H-5), 2.5 (t, J=6.4, 2H, H-3), 2.85 (m, 1H, H-6), 3.35 (m, 1H, H-6), 6.0 (br, 1H, COOH), 6.3 (s, 1H, N-CH-CO), 7.3-7.5 (m, 5H, Ph). Anal. Calcd for C₁₃H₁₅NO₃: C, 66.95; H, 6.44; N, 6.01. Found: C, 66.76; H, 6.49; N, 5.92.

Reaction of compounds (10a,c) with *N*-phenylmethylenbenzenesulfonamide

General method: A solution of **10a** or **10c** (5 mmol) in acetic anhydride (5 mL) was heated at reflux temperature for 1 h under nitrogen. *N*-Phenylmethylenbenzenesulfonamide (1.22 g, 5 mmol) was added and the heating continued for 24 h. After evaporation of the acetic anhydride, the residue was taken up in CH₂Cl₂ (20 mL) and the solution was washed with saturated NaHCO₃ and then with water. The organic

phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel (Toluene/AcOEt = 90/10).

(E)-1-(2-Phenylethenyl)-2-pyrrolidinone (18a): Yield 10%; mp 125 °C (lit.,²⁰ 128 °C).

(E)-1-(1,2-Diphenylethenyl)-2-pyrrolidinone (18c): Yield 25%; mp 143-145 °C (toluene). $^1\text{H-NMR}$: δ 2.15 (m, 2H, H-4), 3.2 (t, $J=7.1$, 2H, H-3), 3.55 (t, $J=7.2$, 2H, H-5), 6.9 (s, 1H, =CHPh), 7.1-7.5 (m, 5H, Ph). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}$: C, 82.13; H, 6.46; N, 5.32. Found: C, 82.04; H, 6.45; N, 5.12.

Reaction of compounds (9-11,a-c) with dimethyl acetylenedicarboxylate, ethyl propiolate or 1,3-diphenylpropynone

General method: A solution of substrates (9-11,a-c) (3 mmol) in acetic anhydride (5 mL) was heated at reflux temperature for 1 h under nitrogen. Dimethyl acetylenedicarboxylate (0.43 g, 3 mmol), ethyl propiolate (1.47 g, 15 mmol) or 1,3-diphenylpropynone (0.62 g, 3 mmol) was added and the heating continued for 3-24 h. After evaporation of the acetic anhydride, the residue was taken up in CH_2Cl_2 (20 mL) and the solution was washed with saturated NaHCO_3 and then with water. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel (Toluene/AcOEt = 90/10).

Dimethyl 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (19a): mp 108-110 °C (iPrOH). $^1\text{H-NMR}$: δ 3.75 (s, 6H, 2 COOCH_3), 4.2 (s, 2H, H-1), 4.95 (s, 2H, H-3), 7.2 (s, 1H, H-5). $^{13}\text{C-NMR}$: δ 29.99 (t, C-1), 48.94 (t, C-3), 51.33 (q, OCH_3), 51.46 (q, OCH_3), 120.42 (s, C-7a), 121.4 (d, C-5), 142.62 (2s, C-6 and C-7), 163.55 (2s, 2 CO). IR (nujol): ν 1733.0 cm^{-1} (COOCH_3). MS (70eV, EI): m/z 241 [M^+], 209, 182, 164, 151, 123. Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_4\text{S}$: C, 49.79; H, 4.56; N, 5.81. Found: C, 49.56; H, 4.59; N, 5.61.

Dimethyl 5-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (19b): mp 134 °C (lit.,²¹ 135 °C).

Dimethyl 5-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (19c): mp 112-113 °C (iPrOH). $^1\text{H-NMR}$: δ 3.65 (s, 3H, COOCH_3), 3.75 (s, 3H, COOCH_3), 4.3 (s, 2H, H-1), 4.85 (s, 2H, H-3), 7.3-7.4 (m, 5H, Ph). $^{13}\text{C-NMR}$: δ 29.92 (t, C-1), 48.38 (t, C-3), 51.31 (q, OCH_3), 51.81 (q, OCH_3), 105.6 (s, C-5), 117.07 (s, C-7a), 128.42 (d, Ph), 128.59 (d, Ph), 128.99 (d, Ph), 129.77 (s, Ph), 130.92 (s, C-6), 140.98 (s, C-7), 161.18 (s, CO), 162.88 (s, CO). IR (nujol): ν 1712.77 cm^{-1} (COOCH_3). MS (70eV, EI): m/z 317 [M^+], 285, 256, 240, 227, 199. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4\text{S}$: C, 60.56; H, 4.73; N, 4.41. Found: C, 60.34; H, 4.49; N, 4.28.

Dimethyl 2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate (20a): mp 87 °C (lit.,²² 86.5 °C).

Dimethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate (20b): mp 102 °C (lit.,²³ 103 °C).

Dimethyl 5-phenyl-2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate (20c): mp 158 °C (lit.,²⁴ 158 °C).

Dimethyl 5,6,7,8-tetrahydro-1,2-indolizinedicarboxylate (21a):²⁵ mp 80-81 °C (iPr₂O). ¹H-NMR: δ 1.8, 1.9 (2 m, 4H, H-6 and H-7), 2.95 (t, J=6.49, 2H, H-8), 3.85 (t, J=6.02, 2H, H-5), 6.9 (s, 1H, H-3). Anal. Calcd for C₁₂H₁₅NO₄: C, 60.76; H, 6.33; N, 5.91. Found: C, 60.44; H, 6.39; N, 5.88.

Dimethyl 3-methyl-5,6,7,8-tetrahydro-1,2-indolizinedicarboxylate (21b): mp 85 °C (lit.,²⁶ 86 °C).

Dimethyl 3-phenyl-5,6,7,8-tetrahydro-1,2-indolizinedicarboxylate (21c): mp 125 °C (lit.,²⁷ 126 °C).

Ethyl 5-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate (22b) and ethyl 5-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylate (25b): The structure of these compounds, not stable, was determined by the NMR spectral data of their mixture. **22b** ¹H-NMR: δ 1.3 (t, J=7.13, 3H, OCH₂CH₃), 2.5 (s, 3H, CH₃), 4.0 (s, 2H, H-1), 4.2 (q, J=7.13, 2H, OCH₂CH₃), 4.85 (s, 2H, H-3), 6.25 (s, 1H, H-7). **25b** ¹H-NMR: δ 1.4 (t, J=7.14, 3H, OCH₂CH₃), 2.2 (s, 3H, CH₃), 4.3 (s, 2H, H-1), 4.45 (q, J=7.14, 2H, OCH₂CH₃), 4.9 (s, 2H, H-3), 6.3 (s, 1H, H-6).

Ethyl 5-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate (22c) and ethyl 5-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylate (25c): These compounds are not stable; they were obtained as an oil. **22c** ¹H-NMR: δ 1.15 (t, J=7.13, 3H, OCH₂CH₃), 4.1 (s, 2H, H-1), 4.15 (q, J=7.13, 2H, OCH₂CH₃), 4.85 (s, 2H, H-3), 6.45 (s, 1H, H-7). Anal. Calcd for C₁₅H₁₅NO₂S: C, 65.93; H, 5.49; N, 5.13. Found: C, 65.98; H, 5.32; N, 5.05. **25c** ¹H-NMR: δ 1.35 (t, J=7.12, 3H, OCH₂CH₃), 4.3 (q, J=7.12, 2H, OCH₂CH₃), 4.35 (t, J=1.44, 2H, H-1), 5.15 (t, J=1.44, 2H, H-3), 6.75 (s, 1H, H-6). Anal. Calcd for C₁₅H₁₅NO₂S: C, 65.93; H, 5.49; N, 5.13. Found: C, 65.88; H, 5.28; N, 4.98.

Ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-6-carboxylate (23b)²⁸ and ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (26b). **23b:** oil. ¹H-NMR: δ 1.32 (t, J=7.14, 3H, OCH₂CH₃), 2.45 (s, 3H, CH₃), 2.5 (m, 2H, H-2), 2.8 (t, J=7.0, 2H, H-1), 3.85 (t, J=7.0, 2H, H-3), 4.25 (q, J=7.14, 2H, OCH₂CH₃), 6.15 (s, 1H, H-7). **26b:** mp 53-55 °C (hexane). ¹H-NMR: δ 1.30 (t, J=7.13, 3H, OCH₂CH₃), 2.2 (s, 3H, CH₃), 2.5 (m, 2H, H-2), 3.05 (t, J=7.2, 2H, H-1), 3.85 (t, J=7.2, 2H, H-3), 4.25 (q, J=7.13, 2H,

OCH₂CH₃), 6.25 (s, 1H, H-6). Anal. Calcd for C₁₁H₁₅NO₂: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.28; H, 7.66; N, 7.09.

Ethyl 5-phenyl-2,3-dihydro-1H-pyrrolizine-6-carboxylate (23c) and ethyl 5-phenyl-2,3-dihydro-1H-pyrrolizine-7-carboxylate (26c). **23c:** mp 74-75 °C (cyclohexane). ¹H-NMR: δ 1.15 (t, J=7.10, 3H, OCH₂CH₃), 2.45 (m, 2H, H-2), 2.85 (t, J=7.2, 2H, H-1), 3.85 (t, J=7.2, 2H, H-3), 4.15 (q, J=7.13, 2H, OCH₂CH₃), 6.4 (s, 1H, H-7), 7.3-7.5 (m, 5H, Ph). Anal. Calcd for C₁₆H₁₇NO₂: C, 75.29; H, 6.67; N, 5.48. Found: C, 75.19; H, 6.59; N, 5.38. **26c:** mp 91-92 °C (cyclohexane). ¹H-NMR: δ 1.3 (t, J=7.11, 3H, OCH₂CH₃), 2.55 (m, 2H, H-2), 3.1 (t, J=6.95, 2H, H-1), 4.15 (t, J=6.95, 2H, H-3), 4.35 (q, J=7.11, 2H, OCH₂CH₃), 6.8 (s, 1H, H-6), 7.3-7.5 (m, 5H, Ph). Anal. Calcd for C₁₆H₁₇NO₂: C, 75.29; H, 6.67; N, 5.48. Found: C, 75.26; H, 6.72; N, 5.43.

Ethyl 3-methyl-5,6,7,8-tetrahydro-2-indolizinecarboxylate (24b)²⁹ and ethyl 3-methyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate (27b):³⁰ The analytical and spectroscopic data agreed with the reported ones.

Ethyl 3-phenyl-5,6,7,8-tetrahydro-2-indolizinecarboxylate (24c) and ethyl 3-phenyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate (27c). **24c:** mp 76-77 °C (iPr₂O). ¹H-NMR: δ 1.1 (t, J=7.12, 3H, OCH₂CH₃), 1.85 (m, 4H, H-6 and H-7), 2.85 (t, J=6.03, 2H, H-8), 3.65 (t, J=5.95, 2H, H-5), 4.1 (q, J=7.12, 2H, OCH₂CH₃), 6.4 (s, 1H, H-1), 7.30-7.45 (m, 5H, Ph). Anal. Calcd for C₁₇H₁₉NO₂: C, 75.84; H, 7.06; N, 5.2. Found: C, 75.66; H, 6.96; N, 5.13. **27c:** mp 70-71 °C (iPr₂O). ¹H-NMR: δ 1.3 (t, J=7.12, 3H, OCH₂CH₃), 1.9 (m, 4H, H-6 and H-7), 3.15 (t, J=6.03, 2H, H-8), 3.9 (t, J=5.43, 2H, H-5), 4.3 (q, J=7.12, 2H, OCH₂CH₃), 6.65 (s, 1H, H-2), 7.25-7.40 (m, 5H, Ph). Anal. Calcd for C₁₇H₁₉NO₂: C, 75.84; H, 7.06; N, 5.2. Found: C, 75.74; H, 6.99; N, 5.15.

(5,6-Diphenyl-1H,3H-pyrrolo[1,2-*c*]thiazol-7-yl)phenylmethanone (28) and (5,7-diphenyl-1H,3H-pyrrolo[1,2-*c*]thiazol-6-yl)phenylmethanone (31): The structure of these compounds, not stable, was determined by the NMR spectral data of their mixture. **28:** ¹H-NMR: δ 4.25 (s, 2H, H-1), 4.95 (s, 2H, H-3), 6.85-7.30 (m, 13H, Ph), 7.5 (d, J=7.35, 2H, H-ortho Ph-CO). **31:** ¹H-NMR: δ 4.2 (s, 2H, H-1), 5.0 (s, 2H, H-3), 6.85-7.30 (m, 13H, Ph), 7.6 (d, J=7.57, 2H, H-ortho Ph-CO).

(2,3-Diphenyl-6,7-dihydro-5H-pyrrolizin-1-yl)phenylmethanone (29): mp 171-173 °C (iPrO₂). ¹H-NMR: δ 2.45 (m, 2H, H-6), 2.9 (t, J=7.27, 2H, H-7), 3.95 (t, J=7.09, 2H, H-5), 6.9-7.0 (m, 5H, Ph), 7.10-

7.30 (m, 8H, Ph), 7.55 (d, J=6.92, 2H, H-orto Ph-CO). Anal. Calcd for C₂₆H₂₁NO: C, 85.95; H, 5.78; N, 3.86. Found: C, 85.84; H, 5.69; N, 3.75.

(1,3-Diphenyl-6,7-dihydro-5H-pyrrolizin-2-yl)phenylmethanone (32): mp 213-214 °C (iPrO₂). ¹H-NMR: δ 2.5 (m, 2H, H-6), 3.0 (t, J=7.09, 2H, H-7), 4.0 (t, J=7.01, 2H, H-5), 6.95-7.30 (m, 13H, Ph), 7.65 (d, J=6.98, 2H, H-ortho Ph-CO). Anal. Calcd for C₂₆H₂₁NO: C, 85.95; H, 5.78; N, 3.86. Found: C, 85.82; H, 5.66; N 3.73.

(2,3-Diphenyl-5,6,7,8-tetrahydroindolizin-1-yl)phenylmethanone (30) and (1,3-diphenyl-5,6,7,8-tetrahydroindolizin-2-yl)phenylmethanone (33): The structure of these compounds, not separable by column chromatography, was determined by the NMR spectral data of their mixture. **30:** ¹H-NMR: δ 1.9 (m, 4H, H-6 and H-7), 3.1 (t, J=6.39, 2H, H-8), 3.8 (t, J=5.79, 2H, H-5), 6.80-7.30 (m, 13H, Ph), 7.55 (d, J=7.11, 2H, H-ortho Ph-CO). **33:** ¹H-NMR: δ 1.9 (m, 4H, H-6 and H-7), 2.9 (t, J=7.02, 2H, H-8), 3.9 (t, J=5.85, 2H, H-5), 6.80-7.30 (m, 13H, Ph), 7.65 (d, J=7.12, 2H, H-orto Ph-CO).

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