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Synthesis and Transition Metal Catalysed Reactions of 1-Ureido-3-Propargyl-2,3-Dihydropyrrol-2-ols, 1-Ureido-3-Propargylpyrroles and 1-Ureido-3-Propargyl-3-Phosphono-1*H*-Pyrrol-2(3*H*)-ones.

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Abstract: The title compounds were obtained by reaction of conjugated azoalkenes with activated methinic derivatives bearing a propargylic residue. 1-Ureido-3-propargyl-2,3-dihydropyrrol-2-ols gave in the presence of Cu(I) catalyst the 2,5-dimethyl-3-ethoxycarbonyl-4-(2-oxopropyl)-1-(N'-phenylureido)-pyrrole, while in the presence of Pd(0) or Au^{3+} the 3,6-dimethyl-5-ethoxycarbonyl-4-propargyl-1,4-dihydropyridazine was obtained by ring opening and ring expansion reaction. The propargylic side chain of 1-ureido-3-propargylpyrroles and 1-ureido-3-propargyl-3-phosphono-1*H*-pyrrol-2(3*H*)-ones was functionalised by means of palladium and/or copper catalysed coupling reactions with aryl or vinyl triflates and halides.

INTRODUCTION

In connection with our ongoing activity aimed at developing a general synthetic strategy to reach directly polyfunctionalized pyrrole derivatives from conjugated azoalkenes,[1] we examined the reaction between these latter substrates with easily available 2-propargyl-1,3-dicarbonyl compounds[2] and triethyl α-propargylphosphonoacetate in order to achieve new interesting 1-ureido-3-propargyl-2,3-dihydropyrrol-2-ols, 1-ureido-3-propargylpyrroles and 1-ureido-3-propargyl-3-phosphono-1*H*-pyrrol-2(3*H*)-ones. The synthesis of polysubstituted pyrroles itself remains an attractive goal as they occur in biological, pharmaceutical and organic chemistry.[3] Also pyrrolinone ring systems are very attractive as they are effective in the synthesis of bile pigments and related compounds.[4] Moreover the reported procedures for the synthesis of similar derivatives bearing propargylic substituents require multistep and tedious procedures involving the handling of very toxic pyrrylthallium compounds[5].

Alkynyl substituted heterocycles are useful intermediates in organic synthesis as the alkynyl moiety can easily provide new carbon-carbon and carbon-heteroatom bonds by means of simple transformations.

The reaction of 1-alkynes with aryl or vinyl triflates and halides, in the presence of a base and a palladium(0) catalyst as well as of copper(I) iodide as co-catalyst, for example, has proven to be very useful for the synthesis of disubstituted acetylene derivatives, as well as for the preparation of a large variety of cyclic and heterocyclic compounds[6].

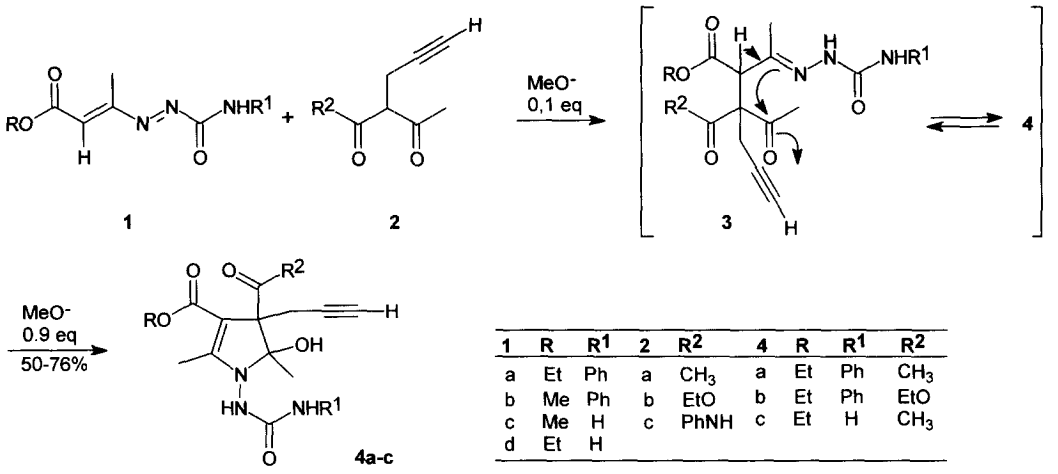
In particular, the reaction of conjugated 1,2-diaza-1,3-butadienes with 2-propargyl-1,3-dicarbonyl compounds provides, through 1,4-conjugate addition followed by intramolecular cyclization process, 1-ureido-3-propargyl-2,3-dihydropyrrol-2-ols and the behaviour of these compounds in intramolecular nucleophilic reactions with transition metal activated carbon-carbon triple bond is discussed. Moreover, the acid-catalyzed aromatization of the 3-acetyl-4-ethoxycarbonyl-2,5-dimethyl-1-(N'-phenylureido)-3-propargyl-2,3-dihydro-pyrrol-2-ol gave the corresponding 2,5-dimethyl-4-ethoxycarbonyl-1-(N'-phenylureido)-3-propargyl-pyrrole and the reaction of 4-methoxycarbonyl-3-methyl-N-phenylcarbamoyl-1,2-diaza-1,3-butadiene with triethyl α-propargyl-phosphonoacetate gave the 3-diethylphosphono-5-methyl-4-methoxycarbonyl-1-(N'-phenylureido)-3-propargyl-1*H*-pyrrol-2(3*H*)-one. In both cases, the propargylic side chain of the pyrrole ring has been connected to singular aliphatic and aromatic moieties by palladium-catalyzed treatment of the starting heterocycles with triflates or halides to give highly substituted 1-ureido-3-alkynyl-pyrroles and 1-ureido-3-alkynyl-3-phosphono-1*H*-pyrrol-2(3*H*)-ones. Finally, an alternative route to 1-ureido-3-alkynyl-3-phosphono-1*H*-pyrrol-2(3*H*)-ones is also proposed *via* an initial coupling reaction with triethyl α-propargyl-phosphonoacetate followed by the reaction of the triethyl α-alkynylphosphonoacetates with conjugated azoalkenes.

RESULTS AND DISCUSSION

Conjugated azoalkenes **1a** and **1d** react with 3-acetyl-5-hexyn-2-one **2a** and with ethyl 2-acetyl-4-pentynoate **2b** in tetrahydrofuran at 0°C and in the presence of sodium methoxide to give 1-ureido-3-propargyl-2,3-dihydropyrrol-2-ols **4a-c** The reaction pattern, outlined in Scheme 1, is in agreement with previously reported results from the reaction of conjugated azoalkenes with β-dicarbonyl compounds and CH-substituted phosphonoacetates.[1] Performing the reactions with triethylamine or potassium carbonate as bases resulted in the isolation of the same reaction products in lower yields.

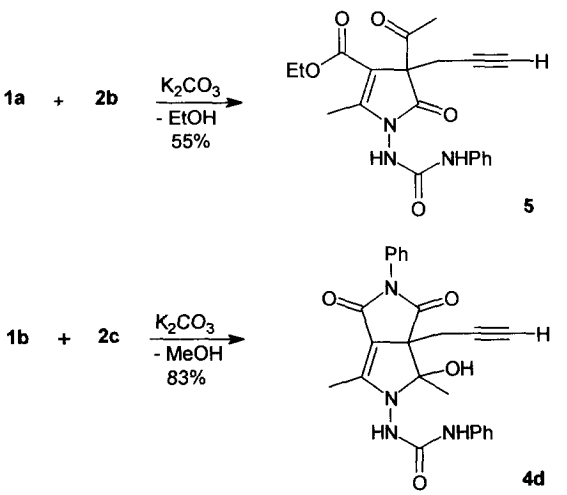
When **1a** was reacted with **2b** in acetonitrile at 45°C using potassium carbonate as base the cyclisation step involves the ester group instead of the keto group and leads to the 1-ureido-3-propargyl-1*H*-pyrrol-2(3*H*)-one **5.** This represents the first case where the cyclisation step involves the ester group even in the presence of the more reactive keto group. A similar behaviour was observed for the reaction between conjugated azoalkenes and ethyl phenylcyanoacetate, the cyclisation step involving the ester function instead of cyano group.[7] Under the same reaction conditions **1b** reacts with **2c** to give, in preparative yields, N-phenyl-[2,5-dimethyl-5-hydroxy-1-(N'-phenylureido)-4-propargyl]-4,5-dihydro-3,4-pyrrolodicarboximide **4d**, which arises

from the initially formed 2,3-dihydropyrrol-2-ol by intramolecular condensation reaction. (Scheme 2, Table 1).



1	R	R^1	2	R^2	4	R	R^1	R^2
a	Et	Ph	a	CH_3	a	Et	Ph	CH_3
b	Me	Ph	b	EtO	b	Et	Ph	EtO
c	Me	H	c	PhNH	c	Et	H	CH_3
d	Et	H						

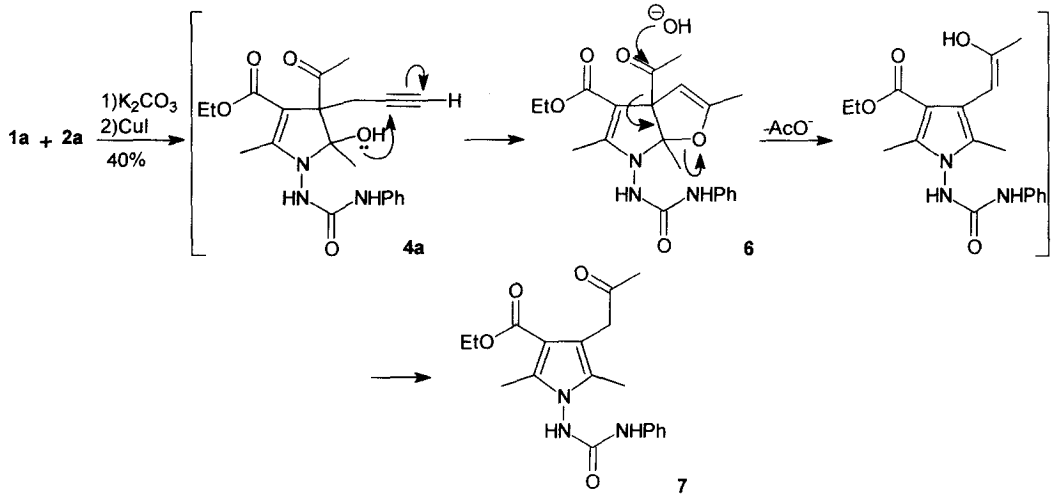
Scheme 1



Scheme 2

The knowledge that a great number of oxygen-containing heterocycles have been prepared by transition-metal catalysed intramolecular reaction starting from alkynes containing oxygen nucleophiles[9] prompted us to test the suitability of 3-propargyl-2,3-dihydropyrrol-2-ols **4a-d** to give condensed heterocyclic rings, which are otherwise difficult to reach, by intramolecular nucleophilic reactions. The reactions were carried out in a basic medium in different solvents (tetrahydrofuran and acetonitrile), over a range of temperatures and in the presence of suitable catalysts: copper(I),[8] palladium(II),[9] gold(III)[10] and palladium(0). When **4a** was treated in

tetrahydrofuran at 60°C in the presence of potassium carbonate and copper(I) iodide as catalyst, it was possible to isolate in moderate yield 2,5-dimethyl-3-ethoxycarbonyl-4-(2-oxopropyl)-1-(N'-phenylureido)-pyrrole **7**, which probably arises from the bicyclic intermediate **6** by action of the base. It is worth noting that **7** was obtained in 40% yield in a one-pot procedure starting from **1a** and **2a**. The reaction, which occurs only in the presence of copper(I), probably proceeds via a tandem-cascade 1,4-conjugated addition, intramolecular heterocyclization and nucleophilic addition of hydroxylic oxygen over a copper(I) activated triple bond, followed by base catalysed ring opening and aromatization to give **7** (Scheme 3). Any attempt to isolate **6** or similar compounds from the reactions performed under the same conditions with dihydropyrroles **4b-d** failed; the crude reaction mixture composed of a complex mixture of unidentified products.

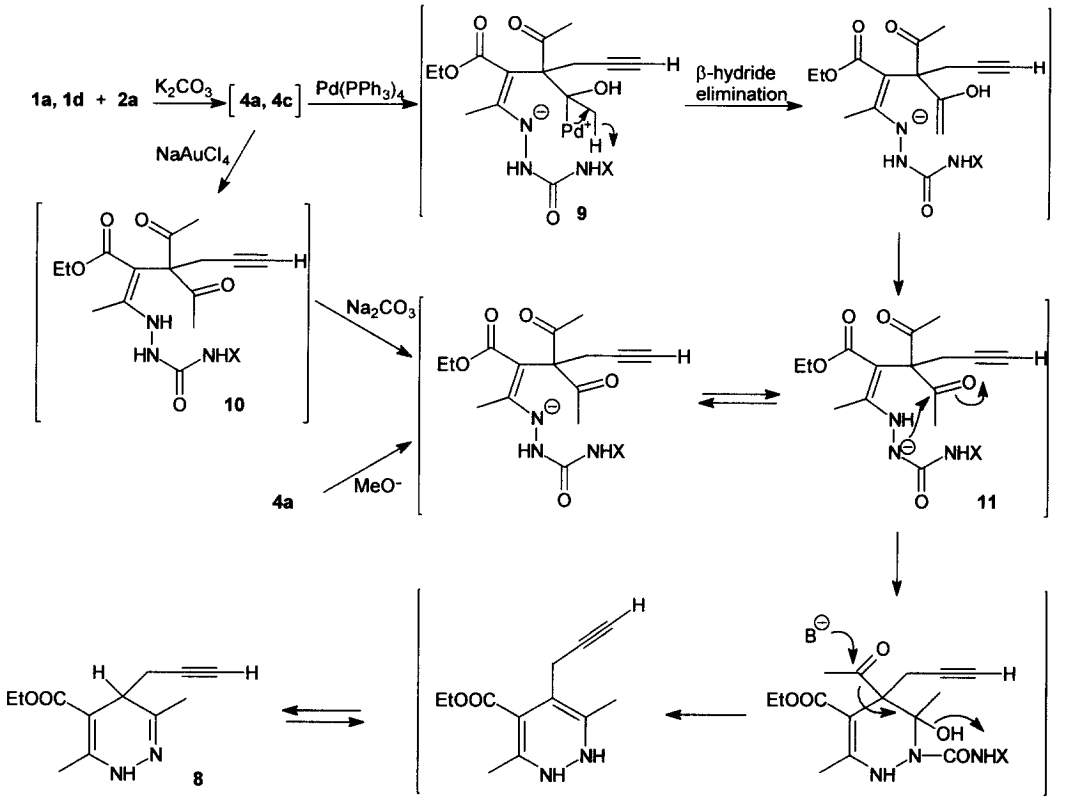


Scheme 3

A different reaction pathway was observed when **4** were treated, in one-pot reactions starting from **1a** or **1d** and **2a**, with $Pd(II)Cl_2$, $NaAu(III)Cl_4$ or $Pd(0)(PPh_3)_4$ catalysts. When $NaAuCl_4$ or $Pd(PPh_3)_4$ were employed, 3,6-dimethyl-5-ethoxycarbonyl-4-propargyl-1,4-dihydropyridazine **8** was isolated from the reaction mixture in 48 and 87% yields respectively, while, using $PdCl_2$ a complex mixture of unidentified products was obtained. Moreover, **8** was isolated in 80% from **4a** in acetonitrile with one equivalent of NaOMe (Scheme 4).

These results can be rationalised by postulating that intermediate **4** interacts with each catalyst in a different way depending upon the nature of the metal. The capability of copper(I) to give insertion reactions with terminal acetylenic substrates[8] probably enhances the reactivity towards intramolecular nucleophilic attack, while Pd(0) catalyses the ring opening[11] through oxidative insertion into the N-C2 bond. In the latter case, the amido anion **9**, by subsequent β-hydride elimination and keto-enol tautomerization, gave the open chain intermediate **11**, which undergoes a heterocyclization process, followed by base-catalysed elimination of the acetyl group and cleavage of the protecting group linked to N-2,[12] to give **8**. This represents the first case

in which a nitrogen containing five membered ring undergoes Pd(0)-catalysed ring opening and ring expansion reactions. However, reports of similar reactions of smaller rings, such as aziridines and azetidines, have appeared recently in the literature.[11] Finally, a soft Lewis acid, such as Au^{3+}, probably causes the opening of the hemi-aminal bond (N-C2) with the formation of the intermediate **10.** The reaction then proceeds *via* base-induced proton abstraction giving rise to the amido anion **11**, which undergoes transformations similar to those described for the Pd(0)-catalysed reaction.

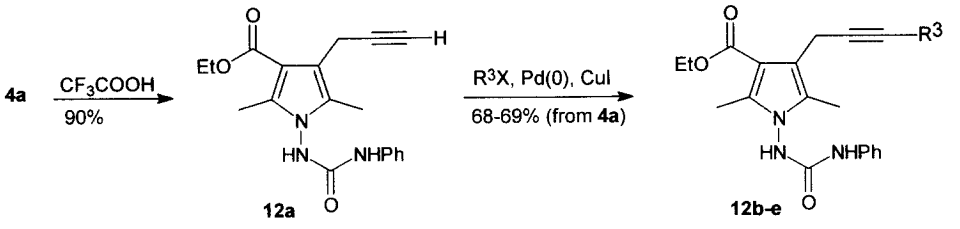


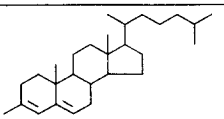
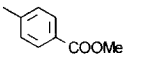
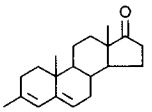
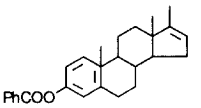
Scheme 4

When **4a** was reacted with $NaAuCl_4$ in the absence of the base, the pyrrole **12a** was isolated in moderate yield (38%). The reaction of **4a** with Pd^{2+} proceeded as reported for the Au^{3+} catalysed reaction and the major acidity[13] of this metal is probably responsible for the formation of complex reaction mixtures. The ring expansion reaction, performed in the absence of catalysis, requires more drastic conditions and **8** was isolated in high yields only when **4a** was treated with NaOMe in CH_3CN. Also, in this case, the reaction proceeds via the intermediate **11**.

Moreover, the 3-propargylpyrrole **12a** (Scheme 5) was prepared in nearly quantitative yield from **4a**, by treatment with trifluoroacetic acid in dichloromethane at -20°C. The propargylic side chain was then functionalized by a coupling reaction[15] with suitable triflate and halide derivatives in

dimethylformamide/potassium carbonate in the presence of palladium(0) as catalyst and copper(I) as co-catalyst, to give, in good yields, the 3-alkynylpyrroles **12b-e** (Scheme 5, Table 1).

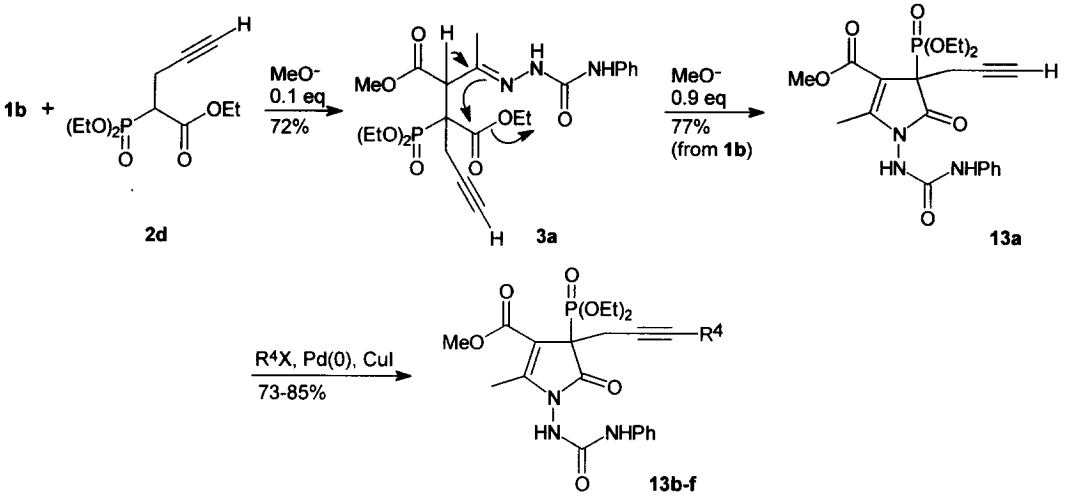


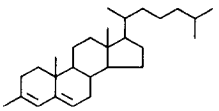
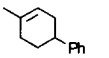
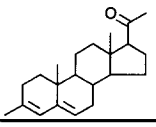
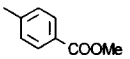
12	R^3	X	12	R^3	X
b		OTf	d		I
c		OTf	e		I

Scheme 5

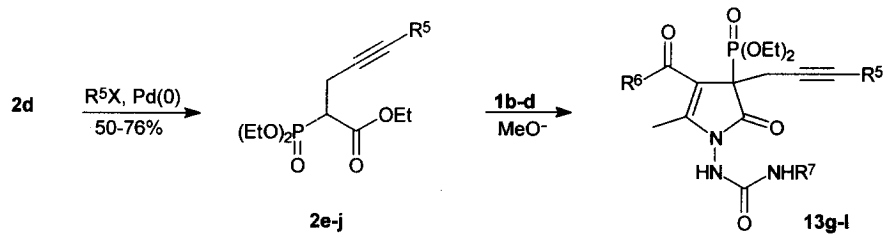
Further extension of these synthetic methodologies was achieved by reacting **1b** with triethyl-α-propargylphosphonoacetate **2d** as previously described for **4a-c.** In this case, the reaction give the 1-ureido-3-propargyl-3-diethylphosphono-(1*H*)-pyrrol-2(3*H*)-one **13a** (Scheme 6, Table 2). The same synthetic approach used to functionalize the propargylic side chain of pyrrole **12a** was applied to the 1*H*-pyrrol-2(3*H*)-one **13a**, which gave the 3-alkynyl-1*H*-pyrrol-2(3*H*)-ones **13b-f** in good yields. Better yields were always obtained using copper(I) iodide as co-catalyst,[14] **13b**, for example, was isolated in 40 % yield using Pd(0) as catalyst and in 70% yield using Pd(0) and copper(I)iodide. Finally, a complementary approach to 1*H*-pyrrol-2(3*H*)-ones **13g-l** has been accomplished by reacting triethyl α-alkynylphosphonoacetates[15] **2e-j** with azoalkenes **1b-d** (Scheme 7, Table 2, 3). Both synthetic procedures of 1-amino-1*H*-pyrrol-2(3*H*)-ones **13b-f** and **13g-l**, represent a useful and easy entry to the desired compounds in good yields (about 60 and 65% respectively, referred to **2d**).

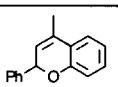
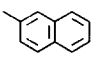
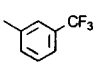
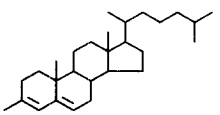
All compounds synthesized in the present work have been characterised with the usual analytical and spectral techniques. In particular, the ^{1}H-NMR spectrum of compounds **13a-l** shows at 2.2-2.5 ppm, two signals (relative intensity 2:1) which can be attributed to the methyl group on C-5. Each signal appears as a doublet by a long-range coupling with phosphorus. The rate of amino-imide conversion for these compounds is slow at room temperature, so that signal for both components can be observed. The rate of amino-imide conversion is affected by solvent and temperature. The ^{1}H-NMR of **13g**, recorded in DMSO-d_6, shows two signals for the methyl group of relative intensity 1:1. When the sample temperature is raised to 80°C, the two peaks collapse in a single signal, split by long range coupling with phosphorus (for data see Table 2).



13	R^4	X	13	R^4	X	13	R^4	X
b		OTf	d		OTf	f		I
c		OTf	e		I			

Scheme 6



1	R^6	R^7	2	13	R^6	R^7	R^5	X	2	13	R^6	R^7	R^5	X
b	OMe	Ph	e	g	OEt	Ph		I	h	j	OEt	H		OTf
c	OMe	H	f	h	OMe	Ph		OTf	i	k	OEt	H		I
d	OEt	H	g	i	OEt	Ph		OTf	j	l	OMe	H		Br

Scheme 7

EXPERIMENTAL

The conjugated azoalkenes **1a-d**[16], β-dicarbonyl derivatives **2a-c**[2] and triflates[17] are known compounds and were prepared according to described methods. All other chemicals and solvents are commercially available and were used without further purification. Nicolet silica gel (0.040-0.063 mm) was employed for flash chromatography. Mps, measured with a Büchi apparatus, are uncorrected. ^{1}H-NMR (200 Mhz) and ^{13}C-NMR (50.3 Mhz) spectra were recorded with a Bruker AC 200 E spectrometer and EI (70eV) and FAB (matrix: glycerol) mass spectra with a TSQ 700 Finnigan/Mat instrument.

1-Ureido-3-propargyl-2,3-dihydropyrrol-2-ols 4a-c and 3-alkynyl-3-diethylphosphono-4-methoxycarbonyl-5-methyl-1-(N'-phenylureido)-1*H*-pyrrol-2(3*H*)-ones 13a, g-l. To a stirred solution of 3-acetyl-5-hexyn-2-one **2a** or ethyl 2-acetyl-4-pentynoate **2b** or α-alkynylphosphonoacetates **2d-j** (1mmol) in THF (3 ml) at 0°C for **2a** and **2b,** and at room temperature for **2d-j**, was added a catalytic amount (10%) of CH_3ONa and then dropwise a solution of appropiate azoalkenes **1a-d** (1mmol) in THF (3 ml). The mixture was stirred for 10 min, until the azoalkene disappeared (TLC). A second amount of CH_3ONa (0.9 mmol) was then added and the reaction mixture stirred for an additional 45 min. Finally, THF was evaporated under reduced pressure without heating, and the crude products purified by flash chromatography (EtOAc/Petroleum ether mixtures) to give pure 2,3-dihydropyrrol-2-ols **4a-c** and 1*H*-pyrrol-2(3*H*)-ones **13a, g-l**. Table 1, 2.

3-Acetyl-4-ethoxycarbonyl-5-methyl-1-(N'-phenylureido)-3-propargyl-1*H*-pyrrol-2(3*H*)-one 5. To a stirred solution of ethyl 3-oxo-2-propargylbutanoate **2b** (168 mg, 1mmol) in CH_3CN (3 ml), was added K_2CO_3 (690 mg, 5 mmol) and then dropwise a solution of conjugated azoalkene **1a** (261 mg, 1 mmol) in CH_3CN (3 ml). The mixture was stirred at 45°C for 1h, the solvent was evaporated under reduced pressure, and the crude product purified by flash chromatography (EtOAc/petroleum ether, 50:50) to give pure **5**. (55%) m.p.: 165-169°C. ^{1}H-NMR (DMSO-d_6/TMS, J=Hz): δ: 1.26 (3H, t, J=7, Me), 2.08 (1H, bs, ≡CH), 2.19 (3H, s, MeCO), 2.50 (3H, s, Me), 2.93 (2H, bs, CH_2≡), 4.23 (2H, q, J=7, CH_2O), 7.05-7.55 (5H, m, Ph), 9.32 and 9.62 (1H, s, NH). ^{13}C-NMR (DMSO-d_6/TMS): δ: 11.54 and 14.01 (Me), 20.84 (*C*H_2-C≡), 25.85 (*Me*CO), 59.92 (CH_2O), 64.31, 73.55 and 78.38 (C≡C, C-3), 104.45 (C-4), 118.85, 122.88, 126.76 and 138.76 (Ph), 154.12 (NHCONH), 158.46 (C-5), 162.33 (*C*O_2Et), 171.50 (CO), 197.47 (*C*OMe). MS, m/z, (%): 383 (M^+, <1), 341 (-CH_2=C=O, 60), 222 (-Ph-N=C=O, 57), 206 (17), 193 (36), 178 (37), 149 (20), 136 (42), 119 (39), 93 (100).

N-Phenyl [2,5-dimethyl-2-hydroxy-1-(N'-phenylureido)-3-propargyl]-2,3-dihydropyrrole-3,4-dicarboximide 4d. To a stirred solution of α-propargylacetoacetanilide **2c** (215 mg, 1mmol) in CH_3CN (3 ml), was added K_2CO_3 (690 mg, 5 mmol) and then dropwise a solution of conjugated azoalkene **1b** (247 mg; 1 mmol) in CH_3CN (3 ml). The mixture was stirred at room temperature for 4h and the crude product purified by flash chromatography (EtOAc or EtOAc/MeOH, 80:20) to give pure **4d**. Table 1.

2,5-Dimethyl-3-ethoxycarbonyl-4-(2-oxopropyl)-1-(N'-phenylureido)pyrrole 7. To a stirred solution of 3-acetyl-5-hexyn-2-one **2a** (276 mg, 2 mmol) in THF (3 ml), was added K_2CO_3 (1.38 g, 10 mmol), and then dropwise a solution of conjugated azoalkene **1a** (522 mg, 2 mmol) in THF (5 ml). The mixture was stirred at room temperature for 90 min and for an additional 30 min at 40°C. Fine powdered CuI (76 mg, 0.4 mmol) was then added to the reaction mixture, which was stirred at 60°C for 3h. The solvent was evaporated under reduced pressure and the crude product extracted with HCl 0.1 N (80 ml)/EtOAc (80 ml). The organic layer was separated and the aqueous phase extracted twice with EtOAc (2 x 50 ml). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give crude **7**, which was purified by flash chromatography (EtOAc/petroleum ether, mixtures). (40%) m.p.: 158-161°C. ^{1}H-NMR (CD_3COCD_3/TMS, J=Hz): δ: 1.27 (3H, t, J= 7, Me), 2.04 (3H, s, Me), 2.10 (3H, s, Me), 2.41 (3H, s, MeCO), 3.65 and 3.80 (1H, d, J= 17, CH_2CO), 4.17 (2H, q, J= 7, CH_2O), 6.96-7.56 (5H, m, Ph). ^{13}C-NMR (CD_3COCD_3/TMS): δ: 9.16, 11.55 and 15.12 (Me), 29.50 (*Me*CO), 41.36 (*CH*$_2$CO), 59.88 (CH_2O), 109.81, 113.09 (C-3/C-4), 120.30, 123.99, 129.08, 129.91, 137.70 and 140.53 (Ph, C-2 and C-5), 155.06 (NHCONH), 166.20 (*C*O_2Et), 206.09 (CO). MS, m/z, (%): 357 (M^+, 22), 339 (-H_2O, 4), 314 (-EtOH, 63), 221 (-PhNHCONH_2, 30), 150 (29), 134 (22), 119 (66), 93 (100).

3,6-dimethyl-5-ethoxycarbonyl-4-propargyl-1,4-dihydropyridazine 8. (Method A). To a stirred solution of 3-acetyl-5-hexyn-2-one **2a** (276 mg, 2 mmol) in CH_3CN (3 ml), was added K_2CO_3 (1.38 g, 10 mmol) and then dropwise a solution of conjugated azoalkene **1a** (522 mg, 2 mmol) or **1d** (370 mg, 2 mmol) in CH_3CN (5 ml). The mixture was stirred at room temperature for 90 min and for an additional 30 min at 40°C. $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) was then added to the reaction of **2a** with **1d**, and $NaAuCl_4$ (32 mg, 0.08 mmol) to the reaction of **2a** with **1a**. In both cases the mixture was stirred at 60°C for 3h. The crude product, obtained as described for pyrrole **7**, was purified by flash chromatography (Petroleum ether/EtOAc, 70:30). Yield: 87% ($Pd(PPh_3)_4$); 48% ($NaAuCl_4$). (Method B). To a stirred solution of 3-acetyl-4-ethoxycarbonyl-2,5-dimethyl-1-(N'-phenylureido)-3-propargyl-2,3-dihydropyrrol-2-ol **4a** (399 mg, 1 mmol) in CH_3CN (3 ml), was added NaOMe (1mmol). The mixture was stirred at room temperature for 1h and the crude product purified as described above. 90% m.p.: 87-89°C. ^{1}H-NMR ($CDCl_3$/TMS, J=Hz): δ: 1.29 (3H, t, J= 7, Me), 1.95 (1H, t, J= 2.8, ≡CH), 2.16 (3H, s, Me), 2.20 (2H, m, CH_2-C≡), 2.28 (3H, s, Me), 3.66 (1H, dd, J= 5.8, 7.2, CH), 4.18 (2H, q, J= 7, CH_2O) , 7.88 (1H, bs, NH). ^{13}C-NMR ($CDCl_3$/TMS): δ: 14.37, 17.70, 20.88, 22.33 (Me, *C*H_2-C≡), 35.67 (C-4), 59.49 (CH_2O), 69.43 (*C*≡CH), 82.27 (C≡*C*H), 91.44 (C-5), 147.69, 149.04 (C-3/C-6), 167.09 (*C*O_2Et). MS, m/z, (%): 220 (M^+, 1.1), 218 (-H_2, 1.4), 181 (-CH_2-C≡CH, 42), 153 (-N_2, 100).

2,5-Dimethyl-4-ethoxycarbonyl-1-(N'-phenylureido)-3-propargylpyrrole 12a. (Method A). To a stirred solution of **4a** (399 mg, 1 mmol) in THF (6 ml) was added $NaAuCl_4$ (34 mg, 0.05 mmol). The reaction mixture was then heated at 40°C for 20h, the solvent was removed under reduced pressure and the crude product purified by crystallization from Et_2O to give pure 2,5-dimethyl-4-ethoxycarbonyl-1-(N'-phenylureido)-3-propargyl-pyrrole **12a**. (38%). (Method B). To a stirred solution of **4a** (399 mg, 1 mmol) in

CH_2Cl_2 (6 ml), cooled at -20°C, was added dropwise trifluoroacetic acid (114 mg, 1 mmol). After 12h at -20°C, the mixture was washed with saturated sodium hydrogen carbonate solution, dried over $MgSO_4$, and evaporated to dryness. (90%). The 2,5-dimethyl-4-ethoxycarbonyl-1-(N'-phenylureido)-3-propargyl-pyrrole **12a** is sufficiently pure to be used without further purification. Recrystallization from ethyl ether gave a sample which was used for analytical pourposes. Table 1.

3-Alkynyl-2,5-dimethyl-4-ethoxycarbonyl-1-(N'-phenylureido)-pyrroles 12b-e and 3-alkynyl-3-diethylphosphono-4-methoxycarbonyl-5-methyl-1-(N'-phenylureido)-1*H*-pyrrol-2(3*H*)-ones 13b-f. To a nitrogen flushed solution of 2,5-dimethyl-4-ethoxycarbonyl-1-(N'-phenylureido)-3-propargyl-pyrrole **12a** or 3-diethylphosphono-5-methyl-4-methoxycarbonyl-1-(N'-phenylureido)-3-propargyl-1*H*-pyrrol-2(3*H*)-one **13a** (1 mmol) in DMF (3ml) were added the appropiate halide or triflate (1 mmol), K_2CO_3 (5 mmol), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol) and CuI (0.04 mmol). The reaction mixture was stirred at 60°C for 3-5h and then extracted with $NaHCO_3$ (sat. sol., 80 ml)/Et_2O (80 ml). The organic layer was separated and the aqueous phase extracted twice with Et_2O (2 x 50 ml). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give crude **12b-e** and **13b-f**, which were purified by flash chromatography (EtOAc/petroleum ether, mixtures). Table 1, 2.

Ethyl 2-diethylphosphono-3-methoxycarbonyl-4-(N'-phenylcarbamoylhydrazono)-2-propargylpentanoate 3a. To a stirred solution of triethyl α-propargylphosphonoacetate **2d** (262 mg, 1 mmol) in THF (3 ml) was added a catalytic amount (10%) of CH_3ONa and then dropwise a solution of conjugated azoalkene **1b** (247 mg; 1 mmol) in THF (3 ml). The mixture was stirred at room temperature until no more azoalkene was detectable by TLC (about 10 min). The solvent was then evaporated under reduced pressure and the crude product was purified by flash chromatography over silica gel column (EtOAc/petroleum ether, 75:25) to give pure **3a**. (72%). ^{1}H-NMR ($CDCl_3$/TMS, J=Hz): δ: 1.29 (9H, m, Me), 1.90 (3H, s, Me), 2.03 (1H, t, J= 2.5, ≡CH), 3.12 and 3.30 (1H, dd, J= 2.5, 16.5, CH_2-C≡), 3.70 (3H, s, MeO), 4.12 (6H, m, CH_2O), 4.36 and 4.41 (1H, s, CH), 6.95-7.75 (5H, m, Ph), 8.40 (1H, s, NH), 9.20 (1H, s, NH). ^{13}C-NMR ($CDCl_3$/TMS, J=Hz): δ: 13.84 (Me), 16.15 (Me), 16.26 (d, J= 3, Me), 16.38 (d, J= 3, Me), 21.23 (d, J= 4, *C*H_2C≡), 52.62 (MeO), 53.66 (d, J= 132, HC-P), 55.07 (d, J= 2, PC*C*H), 62.18 (CH_2O), 63.46 (d, J= 5, $POCH_2$), 63.61 (d, J= 5, $POCH_2$), 71.05 (C≡*C*H), 80.42 (d, J= 9, *C*≡CH), 119.12, 122.92, 128.79 and 138.54 (Ph), 142.99 (d, J= 11, PCCH*C*=), 154.31 (NHCONH), 169.51 (m, CO_2).

Triethyl α-alkynylphosphonoacetates 2e-j. To a nitrogen flushed solution of **2d** (262 mg, 1 mmol) in DMF (3 ml) were added the appropiate halide (2 mmol) or triflate (1 mmol), K_2CO_3 (690 mg, 5 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol). The reaction then proceeds as described for compounds **12b-e** and **13b-f** to give triethyl α-alkynylphosphonoacetates **2e-j**. Table 3.

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Table 1. 1-Ureido-3-propargyl-2,3-dihydropyrrol-2-ols **4a-d** and 1-Ureido-3-alkynyl-pyrroles **12a-e**.

Product	Yield[a] (%)	m.p. (°C)	EI-MS m/z, (%)	^{1}H-NMR δ from TMS, J(Hz)[b]	^{13}C-NMR δ from TMS[b]
4a	76	99-102	399 (M^+, <1), 381(-H_2O, 2), 339 (-AcOH, 68), 310 (61), 217 (310-$PhNH_2$, 44), 204 (339-PhNH-CONH, 69), 191 (310-PhNCO, 52), 176 (82), 93 (100).	1.20 (3H, t, J=7, Me), 1.38 (3H, s, Me) 1.88 (1H, t, J=2, ≡CH), 2.18 (3H, s, Me) 2.21 (3H, s, Me), 2.55 and 2.90 (1H, dd J=2, 18, CH_2-C≡), 4.13 (2H, q, J=7 CH_2O), 5.50 (1H, bs, OH), 6.90-7.5 (5H, m, Ph), 7.73 and 7.78 (1H, bs, NH).	12.02, 14.33 and 19.08 (Me), 23.15 (CH_2), 29.35 (*Me*CO), 60.00 (CH_2O), 63.09 (C-3), 69.11 (*C*≡CH), 83.79 (C≡*C*H), 95.49 (C-2), 104.81 (C-4), 120.32, 124.80, 129.23 and 136.74 (Ph), 157.53 (C-5), 160.60 (NHCONH), 165.13 (CO_2Et), 207.44 (C=O).
4b	57	65-71	429 (M^+, 4), 411 (-H_2O, 12), 372 (411-CH_2-C=CH, 67), 338 (411-CO_2Et, 61), 319 (411-PhNH, 32), 298 (48), 245 (338-$PhNH_2$, 44), 205 (67), 93 (100).	1.24 (3H, t, J=7, Me), 1.64 (3H, s, Me), 2.00 (1H, t, J=2, ≡CH), 2.25 (3H, s, Me), 3.03 and 3.25 (1H, dd, J=2, 18, CH_2-C≡), 4.20 (4H, m, CH_2O), 5.10 (1H, bs, OH), 7.00- 7.40 (6H, m, Ph, NH), 7.80 (1H, bs, NH).	12.07, 14.06, 14.31 and 18.51 (Me), 22.97 (CH_2), 59.89 (CH_2O), 60.52 (C-3), 61.84 (CH_2O), 69.37 (*C*≡CH), 82.72 (C≡*C*H), 95.00 (C-2), 104.91 (C-4), 120.13, 124.02, 129.11 and 137.42 (Ph), 156.72 (C-5), 159.90 (NHCONH), 165.04 (CO_2Et), 170.06(CO_2Et).
4c	74	147-149	323 (M^+, <1), 305 (-H_2O, 18), 280 (-CH_3CO, 33), 263 (-CH_3CO_2H, 81), 262 (-$CH_3CO_2H_2^+$, 100), 234 (91).	1.17 (3H, t, J=7, Me), 1.37 (3H, s, Me), 2.05 (3H, s, Me), 2.15 (1H, t, J=2, ≡CH), 2.21 (3H, s, Me), 2.55 and 2.84 (1H, dd, J=2, 18, CH_2-C≡), 4.09 (2H, q, J=7, CH_2O), 5.40 (1H, bs, OH), 6.50 (2H, bs, NH), 7.94 (1H, bs, NH).[d]	11.80, 14.14 and 18.96 (Me), 21.55 (CH_2), 29.21 (*Me*CO), 58.77 (CH_2O), 62.53 (C-3), 71.17 (*C*≡CH), 82.87 (C≡*C*H), 94.54 (C-2), 100.15 (C-4), 159.16 (C-5), 161.58 (NHCONH), 164.69 (CO_2Et), 207.32 (C=O).[d]
4d	83	169-177	431 (MH^+).[c]	2.19 and 2.26 (3H, s, Me), 2.12 (1H, t, J=2, ≡CH), 2.98 and 3.27 (1H, dd, J=2, 18, CH_2-C≡), 6.95- 7.75 (11H, m, Ph, NH), 10.28 (1H, bs, NH).[d]	14.88 (Me), 23.08 (CH_2), 27.05 (Me), 62.98 (C-3), 73.51 (*C*≡CH), 81.66 (C≡*C*H), 95.00 (C-2), 120.31 (C-4), 119.71, 119.90, 120.31, 123.34, 123. 57, 128.65, 129.06, 137.71 and 139.04 (Ph), 148.20, 149.44, 162.55 and 168.78 (C-5, C=O).[d]
12a	90	158-161	339 (M^+, 34), 310 (-C_2H_5, 30), 176 (-PhNHCON, 20), 119 ($PhNCO^+$, 58), 93 (100).	1.28 (3H, t, J=7, Me), 2.04 (3H, s, Me), 2.31 (3H, s, Me), 2.65 (1H, t, J=2, ≡CH), 3.45 and 3.62 (1H, dd, J=2, 18, CH_2-C≡), 4.18 (2H, q, J=7, CH_2O), 6.92-7.47 (5H, m, Ph), 9.52 and 9.62 (1H, bs, NH).[d]	8.58, 10.81, 14.28 and 14.46 (Me, CH_2), 58.79 (CH_2O), 69.53 (*C*≡CH), 79.17 (C≡*C*H), 106.50/111.70 (C-3/C-4), 118.64, 122.26, 126.81, 128.72, 135.90 and 139.34 (Ph, C-2 and C-5), 154.00 (NHCONH), 164.71 (CO).[d]

12b	68[e]	178-181	705 (M^+, 54), 314 (52), 119 ($PhNCO^+$, 64), 93 (100).	0.68-2.39 (aliph. pattern), 3.63 and 3.84 (1H, d, J=14, CH_2-C≡), 4.28 (2H, q, J=7, CH_2O), 5.37 and 6.13 (1H, bs, H4/H6), 6.90-7.45 (6H, m, Ph, NH), 7.99 (1H, bs, NH).	8.75-42.43 (aliph. pattern), 48.08, 56.14, 56.88, 59.75 (CH_2O), 81.71 and 88.51 (C≡C), 108.00-141.32 ($14Csp_2$), 154.87 (NHCONH), 165.54 (CO).
12c	68[e]	133-137	607 (M^+, <1), 119 ($PhNCO^+$, 34), 93 (100).	0.75-2.55 (aliph. pattern), 3.64 and 3.84 (1H, d, J=14, CH_2-C≡), 4.28 (2H, q, J=7, CH_2O), 5.40 and 6.15 (1H, bs, H4/H6), 6.95-7.45 (6H, m, Ph, NH), 8.14 (1H, bs, NH).	8.86-35.64 (aliph. pattern), 47.72, 48.17, 51.82, 59.67 (CH_2O), 81.39 and 88.91 (C≡C), 108.00-141.42 ($14Csp_2$), 154.96 (NHCONH), 165.43 (COO), 221.32 (CO).
12d	69[e]	191-193	473 (M^+, 75), 444 (-C_2H_5, 88), 351 (444-$PhNH_2$, 54), 325 (444-PhNCO, 37), 338 (-$C_6H_4CO_2CH_3$, 25), 163 (100), 119 ($PhNCO^+$, 64).	1.26 (3H, t, J=7, Me), 2.18 and 2.41 (3H, s, Me), 3.87 (3H, s, OMe), 3.95 and 4.02 (1h, d, J=14, CH_2-C≡), 4.25 (2H, q, J=7, CH_2O), 6.95-7.65 (5H, m, Ph), 7.50 and 7.94 (AA'BB' system, J=6), 9.22 and 9.27 (1H, s, NH).[f]	7.72, 8.85, 13.36 and 15.00 (Me, CH_2), 51.08 (OMe), 58.13 (CH_2O), 77.78 and 93.00 (C≡C), 108.00-139.04 ($16Csp_2$), 153.40 (NHCONH), 164.25 and 165.15 (COO).[f]
12e	68[e]	99-103	695 (M^+, 4), 576 (15) 119 ($PhNCO^+$, 24), 105 ($PhCO^+$, 100).	0.70-2.50 (aliph. pattern), 2.87 and 2.93 (3H, s, Me), 3.64 and 3.85 (1H, d, J=14, CH_2-C≡), 4.26 (2H, q, J=7, CH_2O), 5.87 (1H, bs, H-16)), 6.50-8.30 (15H, m, Ph, NH).	8.83-37.11 (aliph. pattern), 44.43, 47.95, 53.30, 59.47 (CH_2O), 74.38 and 93.00 (C≡C), 108.00-148.59 ($24Csp_2$), 154.84 (NHCONH), 162.89 and 165.15 (COO).

[a] Yield of pure isolated products. Microanalyses were in good agreement with calculated values (C ± 0.3; H ± 0.2; N ± 0.3).
[b] Recorded in $CDCl_3$.
[c] Recorded in FAB mode.
[d] Recorded in DMSO-d_6.
[e] Referred to dihydropyrrole **4a**.
[f] Recorded in DMSO-d_6 / CD_3COCD_3 (1:1).

Table 2. 1-Ureido-3-alkynyl-3-diethylphosphono-1*H*-pyrrol-2(3*H*)-ones **13a-l**.

Product	Yield[a] (%)	m.p. (°C)	EI-MS m/z, (%)	^{1}H-NMR δ from TMS, J(Hz)[b]
13a	77	72-84	463 (M^+, 14), 344 (-PhNCO, 86), 312 (344-MeOH, 91), 207 (344- $PO(OEt)_2$, 100), 119 ($PhNCO^+$, 47).	1.32 (6H, m, Me), 1.90 (1H, m, ≡CH), 2.46 / 2.52 (3H, d, J= 5, Me), 3.15 (1H, dd, J= 5, 16, CH_2-C≡), 3.45 (1H, dd, J= 7, 16, CH_2-C≡), 3.79 (3H, s, MeO), 4.17 (4H, m, CH_2O), 6.90-7.62 (6H, m, Ph, NH), 8.63 (1H, bs, NH)[c]
13b	77	79-95	829 (M^+, <1), 572 (3), 405 (3), 306 (8), 274 (7), 119 (88), 93 (100).	0.50-2.20 (aliph. pattern), 2.45 / 2.53 (3H, d, J= 5, Me), 3.25 (1H, dd, J= 5, 16, CH_2-C≡), 3.58 (1H, dd, J= 7, 16, CH_2-C≡), 3.79 (3H, s, MeO), 4.20 (4H, m, CH_2O), 5.42 and 6.08 (1H, s, H-4/H-6), 6.90- 7.70 (5H, m, Ph)[c]

13c	79	106-118	759 (M^+, <1), 621 (7), 425 (5), 306 (6), 274 (6), 119 (100).	0.60-2.20 (aliph. pattern), 2.45 / 2.52 (3H, d, J= 5, Me), 3.25 (1H, dd, J= 5, 16, CH_2-C≡), 3.55 (1H, dd, J= 7, 16, CH_2-C≡), 3.79 (3H, s, MeO), 4.20 (4H, m, CH_2O), 5.40 and 6.05 (1H, s, H-4/H-6), 6.90-7.75 (5H, m, Ph)[c]
13d	79	76-85	619 (M^+, 7), 481 (22), 425 (23), 362 (24), 231 (24), 217 (48), 119 (100).	1.34 (6H, m, Me), 1.60-1.95 (2H, m, CH_2), 2.05-2.35 (4H, m, CH_2), 2.45 / 2.54 (3H, d, J= 5, Me), 2.50-2.90 (1H, m, CH), 3.25 (1H, dd, J= 5, 16, CH_2-C≡), 3.55 (1H, dd, J= 7, 16, CH_2-C≡), 3.79 (3H, s, MeO), 4.20 (4H, m, CH_2O), 5.97 (1H, bs, CH), 6.90-7.80 (10H, m, Ph)[c]
13e	77	184-187	597 (M^+, 1.5), 473 (10), 340 (19), 305 (19), 277 (26), 217 (26), 119 (100).	1.33 (6H, m, Me), 2.44 / 2.53 (3H, d, J= 5, Me), 3.43 (1H, dd, J= 5, 16, CH_2-C≡), 3.75 (1H, dd, J= 7, 16, CH_2-C≡), 3.80 and 3.88 (3H, s, MeO), 4.15 (4H, m, CH_2O), 6.90-8.00 (9H, m, arom.)[c]
13f	81	59-67	557 (M^+, 9), 465 (11), 433 (37), 406 (35), 300 (63), 217 (75), 119 (95), 93 (100).	1.33 (6H, m, Me), 2.43 / 2.53 (3H, d, J= 5, Me), 3.40 (1H, dd, J= 5, 16, CH_2-C≡), 3.73 (1H, dd, J= 7, 16, CH_2-C≡), 3.80 (3H, s, MeO), 4.20 (4H, m, CH_2O), 6.90-7.65 (9H, m, arom.)[c]
13g	82	74-80	587(M^+, 1), 330 (13), 245 (17), 217 (100), 165 (16), 149 (50).	1.31 (9H, m, Me), 2.42/2.52 (3H, d, J=5, Me), 3.35(1H, dd, J=5, 16, CH_2C≡), 3.65 (1H, dd, J= 7, 16, CH_2-C≡), 4.24 (6H, m, CH_2O), 6.85-7.70 (9H, m, Ph)[c] 1.27 (9H, m, Me), 2.38 / 2.43 (3H, d, J=5, Me), 3.20 and 3.60 (1H, m, CH_2-C≡), 4.15 (6H, m, CH_2O), 7.00-7.60 (9H, m, Ph).[d] 1.27 (9H, m, Me), 2.41 (3H, d, J= 5, Me), 3.20 (1H, dd, J= 5, 16, CH_2-C≡), 3.60 (1H, dd, J= 7, 16, CH_2-C≡), 4.20 (6H, m, CH_2O), 7.00-7.60 (9H, m, Ph), 8.60 and 9.15 (1H, bs, NH)[e]
13h	85	70-82	589 (M^+, 10), 451 (43), 332 (56), 249 (20), 231 (30), 217 (56), 165 (100).	1.31 (6H, m, Me), 2.45 / 2.53 (3H, d, J= 5, Me), 3.41 (1H, dd, J= 5, 16, CH_2-C≡), 3.68 (1H, dd, J= 7, 16, CH_2-C≡), 3.82 (3H, s, MeO), 4.20 (4H, m, CH_2O), 6.90-7.90 (12H, m, arom.)[c]
13i	75	70-82	843 (M^+, 1), 705 (13), 586 (20), 491 (10), 439 (9), 405 (11), 320 (16) , 274 (13), 217 (20), 93 (100).	0.50-2.20 (aliph. pattern), 2.43 / 2.53 (3H, d, J= 5, Me), 3.25 (1H, dd, J= 5, 16, CH_2-C≡), 3.58 (1H, dd, J= 7, 16, CH_2-C≡), 4.20 (6H, m, CH_2O), 5.42 and 6.08 (1H, bs, H-4/H-6), 6.90- 7.70 (5H, m, Ph)[c]
13j	73	72-80	607 (M^+, <1), 532 (6), 489 (9), 363 (26), 244 (100), 217 (29).	1.30 (9H, m, Me), 2.38 / 2.43 (3H, d, J= 5, Me), 3.32 (1H, dd, J= 5, 16, CH_2-C≡), 3.68 (1H, dd, J= 7, 16, CH_2-C≡), 4.20 (6H, m, CH_2O), 5.84 and 5.98 (1H, d, J=4, CH), 6.60- 7.60 (9H, m, arom.)[c]
13k	80	70-82	545 (M^+, 32), 502 (17), 480 (15), 456 (33), 408 (55), 362 (72), 319 (45), 217 (100).	1.31 (9H, m, Me), 2.37 / 2.44 (3H, d, J= 5, Me), 3.32 (1H, dd, J= 5, 16, CH_2-C≡, 3.65 (1H, dd, J= 7, 16, CH_2-C≡), 4.20 (6H, m, CH_2O), 7.25-7.55 (4H, m, Ph)[c]
13l	75	71-80	465 (M^+, 9), 422 (37), 390 (28), 348 (46), 305 (42), 285 (77), 270 (50), 217 (100).	1.34 (6H, m, Me), 2.42 / 2.48 (3H, d, J= 5, Me), 3.38 (1H, dd, J= 5, 16, CH_2-C≡), 3.68 (1H, dd, J= 7, 16, CH_2-C≡), 3.78 (3H, s, MeO), 4.20 (4H, m, CH_2O), 8.62 and 9.01 (1H, s, arom.)[c]

[a] Yield of pure isolated products. Microanalyses were in good agreement with calculated values (C ± 0.3; H ± 0.2; N ± 0.3). [b] Recorded in $CDCl_3$. [c] For details see text. [d] Recorded in DMSO-d_6 at 20°C, for details see text. [e] Recorded in DMSO-d_6 at 80°C, for details see text.

Table 3. Triethyl-α-alkynilphosphonoacetates **2e-j**.

Product	Yield (%)	^{13}C-NMR ($CDCl_3$) δ from TMS, J(Hz)	^{1}H-NMR ($CDCl_3$) δ from TMS, J(Hz)
2e	50	14.2 and 16.4 (Me), 18.1 (d, J= 4, CH_2), 46.3 (d, J=130, CH), 61.7 (CH_2O), 63.1 (CH_2O), 81.0 (d, J=1.5, C≡C), 87.2 (d, J=20, C≡CH), 121.7, 128.5, 132.8 and 133.8 (Ph), 167.8 (d, J=4, C=O).	1.31 (9H, m, CH_3), 2.80-3.35 (3H, m, CH_2-CH), 4.17 (6H, m, CH_2O), 7.30 (4H, m, arom.).
2f	55	14.2 and 16.3 (Me), 18.3 (d, J= 4, CH_2), 45.5 (d, J=130, CH), 61.7 (CH_2O), 63.1 (CH_2O), 82.4 (d, J=1.5, C≡C), 86.3 (d, J=20, C≡C), 120.5, 126.4, 126.5, 127.6, 127.7, 127.8, 128.5, 131.3, 132.8 and 132.9 (arom.), 166.0 (d, J=4, C=O).	1.33 (9H, m, CH_3), 2.85-3.45 (3H, m, CH_2-CH), 4.21 (6H, m, CH_2O), 7.30-7.45 (4H, m, arom.), 7.65-7.90 (3H, m, arom.).
2g	70	11.0-48.0 (aliph. pattern), 56.50 (d, J= 35, CH), 61.56 (CH_2O), 62.70 and 63.00 (d, J= 6, CH_2O), 84.1 (d, J=1.5, C≡C), 85.4 (d, J=20, C≡C), 117.0, 125.7, 134.9 and 141.1 (C3, C4, C5 and C6), 167.9 (d, J=4, C=O).	0.60-2.30 (aliph. pattern), 2.65-3.30 (3H, m, CH_2-CH), 4.18 (6H, m, CH_2O), 5.42 and 6.15 (1H, bs, H-4 / H6).
2h	76	14.1 and 16.4 (Me), 18.1 (d, J= 3, CH_2), 45.3 (d, J=130, CH), 61.7 (CH_2O), 63.1 (CH_2O), 76.8 (d, J= 1.5, C≡C), 89.4 (d, J=20, C≡CH), 167.7 (C=O).	1.30 (9H, m, CH_3), 2.60-3.40 (3H, m, CH_2-CH), 4.16 (6H, m, CH_2O), 5.86 and 6.01 (1H, d, J=4, =CH-CH-Ph), 6.75-7.70 (9H, m, arom.).
2i	74	14.2 and 16.4 (Me), 18.2 (d, J= 4, CH_2), 46.4 (d, J=130, CH), 61.9 (CH_2O), 63.2 and 63.4 (d, J= 6, CH_2O), 80.8 (d, J=1.5, C≡C), 88.31 (d, J=20, C≡C), 121- 135 (Ph), 167.9 (d, J=4, CO).	1.36 (9H, m, CH_3), 2.85-3.45 (3H, m, CH_2-CH), 4.21 (6H, m, CH_2O), 7.30-7.75 (4H, m, arom.).
2j	72	14.2 and 16.4 (Me), 18.1 (d, J= 3, CH_2), 44.8 (d, J=130, CH), 75.5 (d, J=1.5, C≡C), 94.0 (d, J=20, C≡C), 119.7, 156.6 and 158.8 (arom.), 167.5 (d, J=4, C=O).	1.37 (9H, m, CH_3), 2.90-3.40 (3H, m, CH_2-CH), 4.22 (6H, m, CH_2O), 8.72 (2H, s, arom.), 9.11 (1H, s, arom.).

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