DOI: 10.1002/ejoc.201000371

Addition/Cycloaddition of Acetylenedicarboxylates to Open-Chain or Cyclic Amino Carbonyl Compounds

Giacomo Guerrini[a] and Fabio Ponticelli*[a]

Keywords: Cycloaddition / Michael addition / Heterocycles / Substituent effects

Some new, interesting, and unknown heterocyclic rings and open-chain molecules have been obtained with ease and under mild conditions by reaction of a wide range of amino carbonyl compounds with acetylenic esters. The reactivity is highly dependent on the substituents and their positions in the starting material, which can be either cyclic (pyrazolones) or open-chain compounds.

Introduction

Dialkyl acetylenedicarboxylates (DAADs) have been investigated in the past for their high reactivity towards a great variety of organic substrates. Diels–Alder reactions and 1,3-dipolar and [2+2] cycloadditions have been reported as key steps for access to a large class of molecules. Good selectivity of the attack is an "added value", which renders these synthetic protocols of wide interest for the preparation of natural and/or biologically active compounds.[1] In addition, differently substituted pyrroles can be prepared by a two-step reaction (Michael-like addition and elimination) of DAADs on amino carbonyl derivatives.[2]

On the other hand, the tendency of amino carbonyl derivatives to dimerize limits their practical use in syntheses. Following a similar approach, in the present work we wish to present the reactivity of DAADs towards polyfunctional amines **A** and differently substituted pyrazolones **B** and **C** (Figure 1), whose structures contain, beside the nucleophile amino group, two potential sites of attack, the C=O and C=N groups, with the aim to verify the possibility to prepare rare bicyclic heterocycles and to evaluate the factors affecting the nature of the reaction processes.

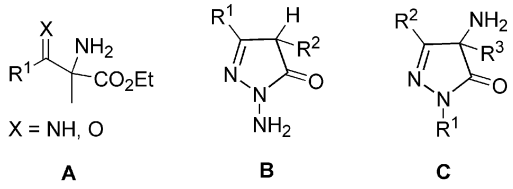


Figure 1. Structures of amino carbonyl compounds used.

[a] Dipartimento di Chimica, Università degli Studi di Siena, Via A. Moro 2, 53100 Siena, Italy
Fax: +39-0577-234254
E-mail: ponticelli@unisi.it

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000371.

Results and Discussion

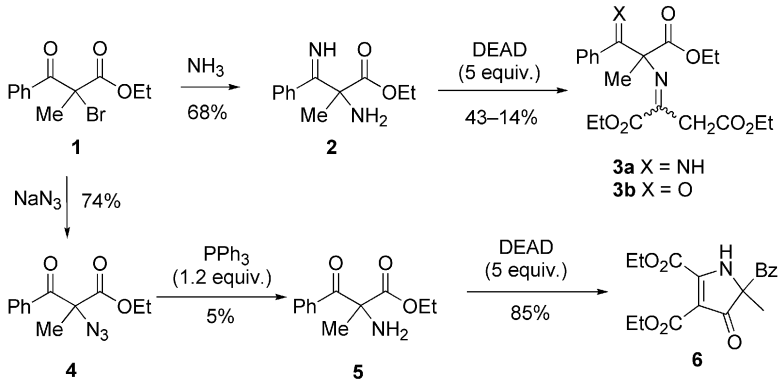
Recently, the interest in amino ketones in synthetic organic chemistry was underlined.[3] To verify the potentiality of the reaction of DAADs with these kinds of compounds, we prepared compounds **2** and **5** according to Scheme 1.

Reaction of bromo ester **1** with ammonia gave nucleophilic substitution and carbonyl condensation product **2** in good yields. On the other hand, amino keto ester **5** was obtained from ester **1** by reduction of azide **4** with triphenylphosphane. Different results were obtained when compounds **2** or **5** were treated with DEAD (diethyl acetylenedicarboxylate). In fact, only Michael-like attack of the alkyne on the amino group of **2** occurred, followed by hydrogen shift from nitrogen to carbon to give isomeric imines **3a**. During chromatographic separation, corresponding ketone **3b** was also obtained. On the other hand, starting from amino keto ester **5**, a different process was found. In fact, in this case, attack on both the amino and ester groups resulted in the formation of pyrrolinone **6**, whose structure was confirmed by single-crystal X-ray diffraction (Figure 2). Afterwards, 1-aminopyrazole derivatives were considered.

As expected, reaction of DMAD (dimethyl acetylenedicarboxylate) with methoxy derivative **7a** (Scheme 2) occurred only at the amino group, giving corresponding imine **8**, whose structure was mainly assigned on the basis of signals at 3.92 ppm and 37.12 ppm in the ^{1}H and ^{13}C NMR spectra, respectively, attributable to a methylene group.

On the other hand, reaction of tautomerizable compound **7b** gave a complex mixture of compounds, from which by repeated chromatographic column separation compound **9** was obtained in 30% yield. Final structure assignment of this compound was achieved by single-crystal X-ray analysis (Figure 3).

For compounds **10a** and **10b** the formation of a bicyclic molecule could be expected, and in this case, the structure



Scheme 1.

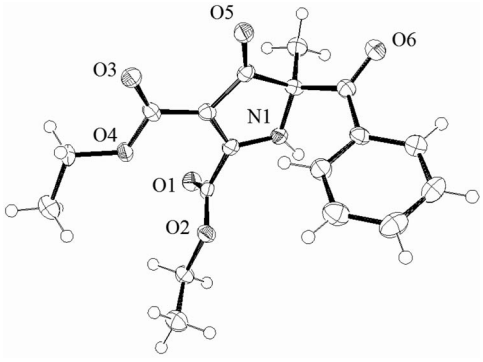


Figure 2. ORTEP drawing of compound **6**.

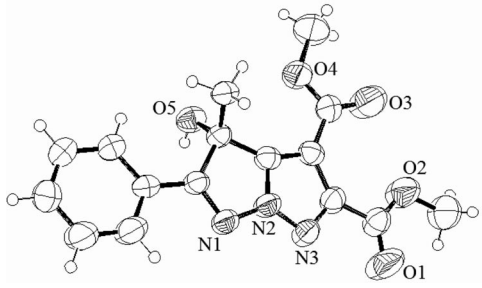
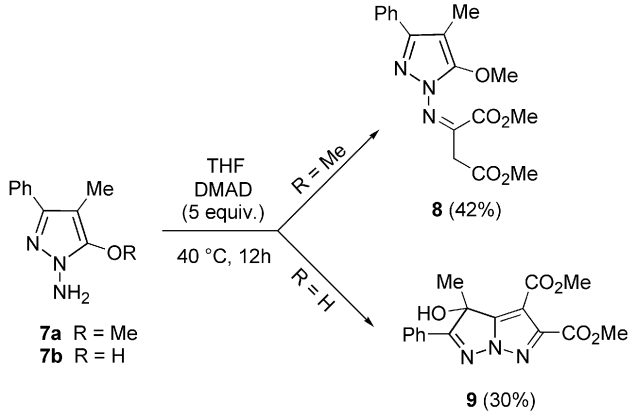
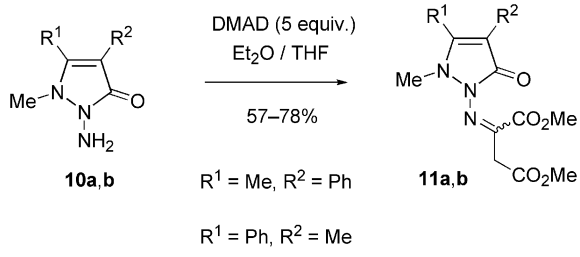


Figure 3. ORTEP drawing of compound **9**.



Scheme 2.

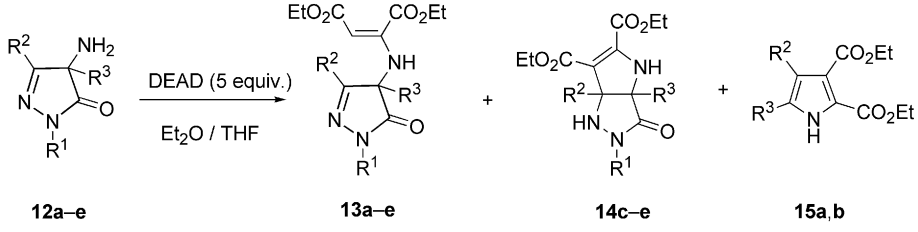
of the pyrazolone is not aromatic. However, in this case the only observed products were the Michael-like products with the formation of compounds **11a** and 11**b** (Scheme 3).



Scheme 3.

Finally, treatment of 4-aminopyrazolones **12a–e** with DEAD, followed by column chromatography, gave three types of compounds in different yields according to the substituents and the reaction conditions (Scheme 4 and Table 1).

The structures of **13a–e** followed from analytical and spectroscopic data. Maleate stereochemistry is based on previous reports of analogous compounds, in particular on the chemical shift of the olefinic proton at about 5.50 ppm in the ^{1}H NMR spectrum.[4] In addition, Overhauser corre-



Scheme 4.

Table 1. Treatment of 4-aminopyrazolones **12a**–**e** with DEAD.

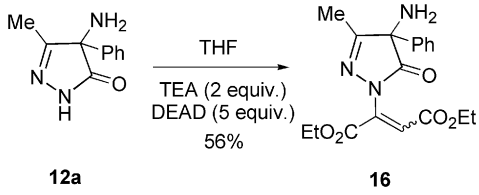
	R^1	R^2	R^3	Yield [%][a]		
				13	**14**	**15**
12a	H	Me	Ph	45	–	13
12b	H	Ph	Me	74	–	13
12c	Me	Ph	Me	58	25	–
12d	Me	Me	Ph	85	10	–
12e	Bn	Me	Ph	69	trace	trace

[a] Isolated yields after column chromatography.

lations were found between the olefinic CH proton and the R^2 substituent group, which provides further evidence for the (*E*) double bond geometry. X-ray analysis of compound **14c** gave the assignment reported in Figure 4, and the structures of **14d** and **14e** were assigned on the basis of analogy with spectroscopic data of **14c**.

To gain more insight into the above reaction, we verified that in the ^{1}H NMR spectra of the crude reaction mixtures, the signals of compounds **13** and **15** were practically absent, whereas the presence of compounds **14** was deduced according to a series of NMR signals. These series of NMR signals were particularly recognizable for compounds with R^2 = methyl. In fact, molecules **12a**, **12d**, and **12e** have a C3 carbon atom of the ring that passes from sp^2 to sp^3 hybridization. This NMR shift of the methyl group from about 2.0 ppm in the starting material and in the open-structured molecules **13** to about 1.0 ppm in the bicyclic compounds is well detectable. On this basis, we can infer that compounds **13** and **15** are formed in a second time and/or during chromatographic separation. As confirmation, compound **14d** kept in a chloroform solution exposed to air, quantitatively decomposes to **13d** and **15a** in an approximately stoichiometric ratio.

Useful insight into the formation mechanism of compounds **13** follows from these considerations. The first is that starting from aminopyrazolone **12a** (Scheme 5), which was treated with triethylamine to afford the corresponding triethylammonium salt on the acidic hydrogen atom, the reaction occurred on the nitrogen atom (N1) of the ring, which under these conditions is the most electron-rich site for the Michael reaction. For reaction with DEAD, Michael attack provided compound **16**, without further cyclization driven by the presence of the heterocyclic carbonyl group.



12a **16**

Scheme 5.

A second useful insight into the reaction mechanism is based on the reactivity of 1-acetyl-4-aminopyrazolone **20** toward the DAADs. Bromination of 1-acetylpyrazolone **17** afforded **18** (Scheme 6), which upon treatment with sodium azide gave **19**. Compound **19** then underwent reduction with molecular hydrogen to afford **20** in good yields. Treatment of **20** with DMAD or DEAD gave exclusively (Scheme 7) bicyclic compounds **21a** or **21b**, which are stable and isolable by column chromatography. The structures of these products are strongly suggested by their NMR properties; in particular, the signal for the C=O group is lacking in the ^{13}C NMR spectrum, and a signal for a nonolefinic CH group at about 4.70 ppm is visible in the ^{1}H NMR spectrum and in DEPT experiments. In the case of **21b**, X-ray analysis gave definitive support to the assignment (Figure 5).

A rationale of all these results can be at this point proposed. The fact that both pyrazolone **17** and 4-(dimethylamino)-1,4-dimethyl-3-phenylpyrazolone (**22**; Figure 6) are completely unaffected by these reagents suggests that

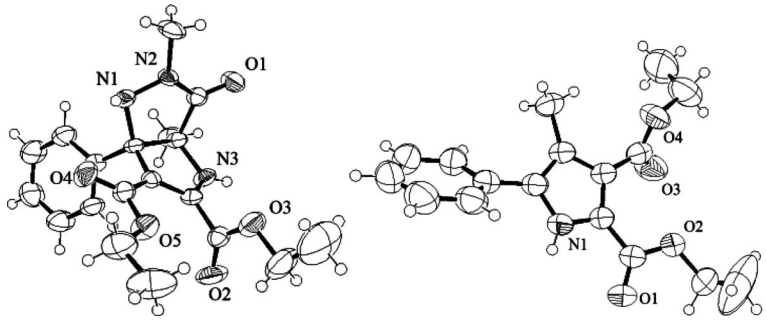
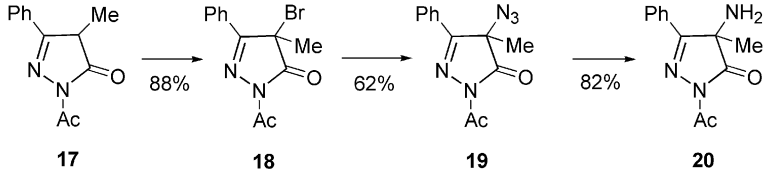
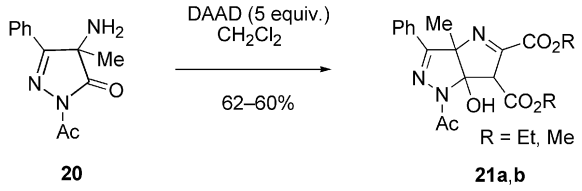


Figure 4. ORTEP drawings of compounds **14c** and **15a**.



17 **18** **19** **20**

Scheme 6.



Scheme 7.

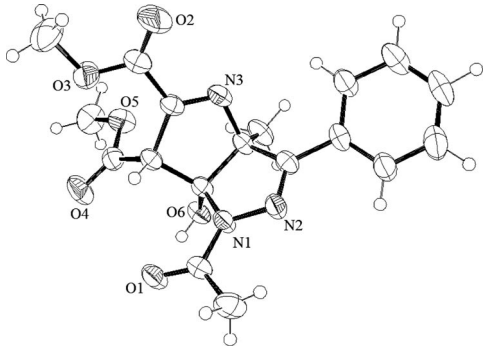


Figure 5. ORTEP drawing of compound **21b**.

the attack on the DAAD firstly (but not for the anion of **12a**) occurs at the acetylenic carbon atom by the NH_2 group. An intermediate zwitterion is formed,[5] which follows different pathways depending on the functional groups present on the substrate. In the case of 4-aminopyrazolones **12a**–**e**, the amino group can at this point act as a pivot system, allowing attack at either the C=O (path i) or C=N (path ii) group (Scheme 8). Path i is the main route followed in every case, and in the presence of an electron-withdrawing group (acetyl) in the 1-position, it is the only operative way. Finally, proton shift gives **14c**–**e**, **21a**,**b**, and **23a**–**e**. Whereas bicyclic compounds **14** are quite stable and usually isolable, the tetrahydropyrrolo[3,2-*c*]pyrazole systems **21** and **23** can be purified by column chromatography only when an acetyl group is present in the 1-position (compounds **21a**,**b**). In the other cases (compounds **23a**–**e**) their presence is supposed, as confirmed by inspection of the NMR spectra of the crude reaction mixtures: the signals at about 4.70 ppm are attributable to the CH group at C6. Compounds **23a**–**e** are then transformed into alkenes **13a**–**e** during chromatographic separation.

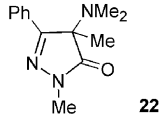
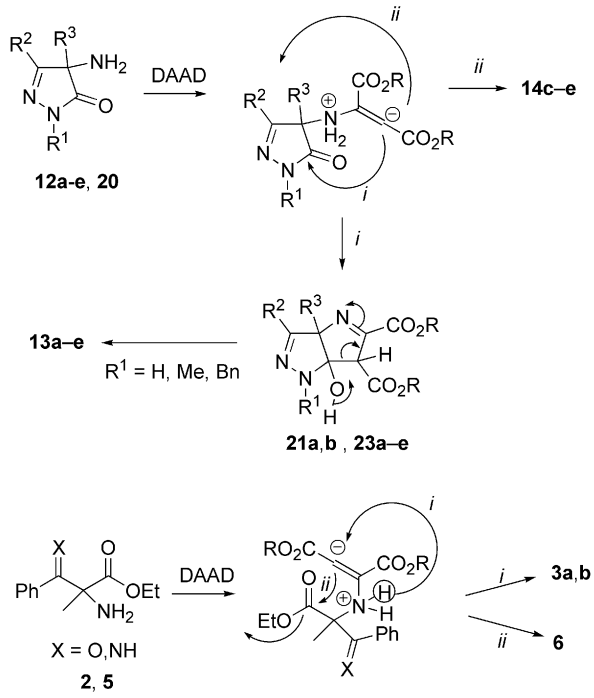
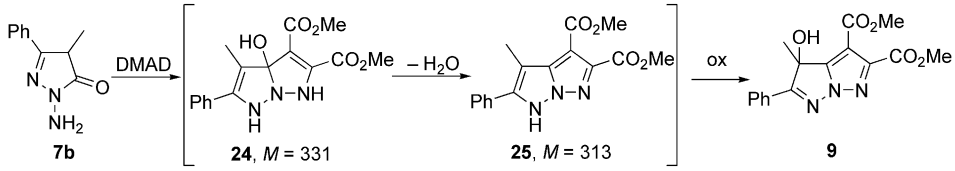


Figure 6. Pyrazolone **22**.



Scheme 8.

Similar processes are also operative for open-chain amino esters **2** and **5**, giving compounds **3a** and **3b** (path i) by proton shift or pyrrolinone **6** (path ii) by exclusive attack on the carbethoxy group followed by loss of EtOH. No attack on the ketonic group was observed. Analogously, 1-aminopyrazole derivatives **7a** and **10a**,**b** are believed to react with DAADs, giving zwitterionic intermediates, which can evolve only by proton shift and rearrangement to the corresponding imines **8** and **11a**,**b**. In the case of compound **7b**, which can exist in three tautomeric forms, a more complex behavior is observed. MS (ESI) analysis of the crude reaction mixture evidenced species with molecular weights *m*/*z* = 331 and *m*/*z* = 313, whereas compound **9** (*m*/*z* = 329) was absent (Scheme 9). DMAD attack on the amino and carbonyl group can account for the formation of bicyclic compound **24**, which then affords **25** by water elimination. Compound **9** is finally formed by oxidation of **25** during chromatographic separation.



Scheme 9.

Conclusions

Acetylenic diesters (DAADs) are highly reactive towards compounds containing both NH_2 and C=X (X = O, NR) moieties. Attack on the amino group and proton shift or reaction on the C=X group give open-chain or cyclic compounds. Chemoselectivity of the process is strongly dependent on the structure and the position of the substituents in the starting substrate. Reaction of DAAD with 1- and 4-aminopyrazolones affords condensed heterocycles **9**, **14**, or **21** of potential biological interest. In fact, they show good structural analogy with some pyrrolopyrazoles recently described as enzymatic inhibitors involved in cancer therapy.[6]

Experimental Section

General: Melting points were determined with a Kofler hot stage. ^{1}H and ^{13}C NMR spectra were recorded at 27 °C ($CDCl_3$), unless otherwise stated, with a Bruker AC200 instrument operating at 200.13 and 50.33 MHz, respectively, or with a Bruker Avance 400 instrument operating at 400.13 and 100.62 MHz, respectively. Chemical shifts are reported in ppm from internal TMS. Pyrazolones **12a**–**e** were synthesized as described in other published works;[7] all other chemicals were of reagent grade and were used without purification. Mass spectra were recorded in the positive or negative ion mode with a LCQ-DECA Thermo instrument by using electrospray ionization. GC–MS experiments were carried out with a Saturn 2000 ion trap (EI, 70 eV) coupled with a Varian 3800 gas chromatograph (Varian, Walnut Creek, CA, USA) equipped with a J&W DB5-MS column (30 m × 0.25 mm ID, 0.25 μm film thickness). All solvents were previously dried according to standard procedures. Analytical TLC was performed on silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel (0.040–0.063 mm).

Ethyl 2-Amino-3-imino-2-methyl-3-phenylpropanoate (2): A solution of **1** (285 mg, 1.00 mmol) in THF (5.0 mL) was cooled to –78 °C and a stream of gaseous ammonia was insufflated until the solution was saturated. The reaction was left to react overnight, to reach room temperature. The crude solution was filtered to eliminate the ammonium bromide solid residue and the solvent was removed under vacuum to give **2**; yield 150 mg (68%); yellow oil. ^{1}H NMR (200 MHz): δ = 1.04–1.11 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.57 (s, 3 H, CH_3), 2.59 (s, 2 H, NH_2), 4.02–4.21 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 7.22–7.49 (m, 3 H, aryl), 7.70–7.79 (m, 2 H, aryl) ppm. ^{13}C NMR: δ = 13.21, 23.00, 61.41, 67.21, 126.21, 127.82, 129.44, 136.23, 172.24, 178.06 ppm. MS (ESI): m/z = 219 $[M - H]^-$. $C_{12}H_{16}N_2O_2$ (220.27): calcd. C 65.43, H 7.32, N 12.72; found C 65.68, H 7.41, N 12.63.

Ethyl 2-Amino-2-methyl-3-oxo-3-phenylpropanoate (5): To a solution of **1**[8] (2.60 g, 9.12 mmol) dissolved in DMF (15 mL) was added sodium azide (0.98 g, 15 mmol). The solution was stirred for 60 min and monitored by TLC (petroleum ether/EtOAc, 7:1). To the resulting crude solution was then added water (10 mL) and diethyl ether (10 mL). The ethereal residue was washed with water (3 × 10 mL) to remove DMF, and the aqueous fraction was extracted with diethyl ether (3 × 10 mL). The organic fractions were dried with $MgSO_4$, and the solvent was evaporated under vacuum to give **4** (1.67 g, 6.76 mmol, 74% yield); light orange oil; R_f = 0.68 (petroleum ether/EtOAc, 7:1). ^{1}H NMR (200 MHz): δ = 1.00–1.07 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.74 (s, 3 H, CH_3), 4.08–4.20 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 7.34–7.59 (m, 3 H, aryl), 7.88–7.93 (m, 2 H, aryl) ppm. MS (ESI): = 248 $[M + H]^+$, 270 $[M + Na]^+$. $C_{12}H_{13}N_3O_3$ (247.25): calcd. C 58.29, H 5.30, N 16.99; found C 58.05, H 5.39, N 17.21. A solution of **4** (420 mg, 1.70 mmol) in THF (10.0 mL) was cooled in an ice bath. To this solution was added triphenylphosphane (524 mg, 2.0 mmol), and the solution was stirred for 3 h without further cooling. Water was added (0.5 mL), and the solvent was evaporated with a nitrogen stream. The resulting crude solution was purified by column chromatography (petroleum ether/EtOAc, 1:1) to afford amino keto ester **5**; yield 19 mg (5%); orange oil. ^{1}H NMR (400 MHz): δ = 0.96–1.03 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.62 (s, 3 H, CH_3), 2.07 (br. s, 2 H, NH_2) 4.11–4.16 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 7.25–7.44 (m, 3 H, aryl), 7.84–7.88 (m, 2 H, aryl) ppm. MS (ESI): m/z = 222 $[M + H]^+$. $C_{12}H_{15}NO_3$ (221.25): calcd. C 65.14, H 6.83, N 6.33; found C 65.04, H 6.99, N 6.54.

4-Amino-1-benzyl-3-methyl-4-phenyl-1,4-dihydropyrazol-5-one (12e): A solution of **12a** (189 mg, 1.0 mmol), benzyl chloride (0.46 mL, 2.0 mmol), and metallic sodium (43 mg, 2.0 mmol) in ethanol (10.0 mL) was stirred and heated at reflux overnight (16 h). The solvent from the resulting violet solution was removed in vacuo, and the crude product was purified by column chromatography (petroleum ether/EtOAc, 1:1) to give **12e**; yield 178 mg (64%); yellow oil; R_f = 0.45 (petroleum ether/EtOAc, 5:3). ^{1}H NMR (200 MHz): δ = 1.81 (s, 3 H, CH_3), 2.19 (br. s, 2 H, NH_2), 4.71–4.93 (q, J = 12.8 Hz, 2 H, CH_2), 7.23–7.36 (m, 10 H, aryl) ppm. ^{13}C NMR: δ = 12.63, 13.84, 20.60, 47.74, 59.95, 67.23, 124.93, 127.39, 127.86, 128.09, 128.32, 128.64, 136.14, 136.23, 162.59, 176.45 ppm. MS (ESI): m/z = 302 $[M + Na]^+$. $C_{17}H_{17}N_3O$ (279,34): calcd. C 73.10, H 6.13, N 15.04; found C 73.38, H 6.03, N 15.28.

1-Acetyl-4-amino-4-methyl-3-phenyl-1,4-dihydropyrazol-5-one (20): Pyrazolone **17** (100 mg, 0.46 mmol), synthesized with excellent yield (97%) according to a given procedure,[9] was brominated with molecular bromine (0.04 mL, 0.78 mmol), which was added dropwise to a stirred solution of chloroform (1.0 mL) without stabilizing ethanol. After 1 h, the solvent was removed with a nitrogen stream, and the oily residue was triturated with diethyl ether to get a solid recognized as **18**; yield 119 mg (88%); pale-yellow solid; m.p. 107–112 °C; R_f = 0.62 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 2.07 (s, 3 H, CH_3), 2.62 (s, 3 H, $COCH_3$), 7.41–7.63 (m, 3 H, aryl), 7.98–8.12 (m, 2 H, aryl) ppm. $C_{12}H_{11}BrN_2O_2$ (295,13): calcd. C 48.84, H 3.76, N 9.49; found C 48.95, H 3.86, N 9.36. To a solution of pyrazolone **18** (87 mg, 0.29 mmol) dissolved in DMF (2.0 mL) was added sodium azide (28 mg, 0.43 mmol). The reaction was stirred for 2 h and monitored by TLC. When the spot corresponding to **18** had disappeared, to the crude solution was added water (10 mL), and the resulting solution was extracted with diethyl ether (3 × 10 mL). The ethereal extracts were dried with $MgSO_4$, and then the solvent was evaporated with a nitrogen stream. The resulting solid corresponded to **19**; yield 46 mg (62%); light-brown solid; m.p. 135–140 °C; R_f = 0.71 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 1.70 (s, 3 H, CH_3), 2.53 (s, 3 H, $COCH_3$), 7.34–7.44 (m, 3 H, aryl), 7.89–7.93 (m, 2 H, aryl) ppm. $C_{12}H_{11}N_5O_2$ (257,25): calcd. C 56.03, H 4.31, N 27.22; found C 55.88, H 4.12, N 26.97. Product **19** (40 mg, 0.16 mmol) was then hydrogenated with molecular hydrogen at atmospheric pressure by using Pd/C (10%, 5 mg) in ethanol solution. The reaction was stirred overnight and monitored by TLC. Upon completion of the reaction, the solvent was removed from the crude solution, and the residue was purified by column chromatography (petroleum ether/EtOAc, 1:2) to obtain **20**; yield 29 mg (82%); white solid; m.p. 123–127 °C; R_f = 0.44 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 1.51 (s, 3 H, CH_3), 2.53 (s, 3 H, $COCH_3$), 7.34–7.44 (m, 3 H, aryl), 8.18–8.22 (m, 2 H, aryl) ppm. MS (ESI):

m/*z* = 232 [M + H]$^+$, 254 [M + Na]$^+$. $C_{12}H_{13}N_3O_2$ (231.25): calcd. C 62.33, H 5.67, N 18.17; found C 62.57, H 5.69, N 18.31.

General Procedure for the Reaction of DAAD with Amino Carbonylic Compounds: To a stirred and warmed solution of amino carbonylic compound was added an excess amount (5:1) of the acetylenic compound. The solution was heated at reflux overnight (16 h) until the starting material disappeared (TLC). After this the solvent was removed in vacuo, and the residue was purified by flash column chromatography (ether petroleum/EtOAc) to give compounds **3a**, **3b**, **6**, **8**, **9**, **11a**, **11b**, **13a**–**e**, **14c**, **14d**, **15a**, **15b**, **16**, **21a**, **21b**.

Diethyl 2-[2-(Ethoxycarbonyl)-1-imino-1-phenylpropan-2-ylimino]-succinate (3a): A solution of **2** (200 mg, 0.90 mmol) and DEAD (0.72 mL, 4.50 mmol) in diethyl ether was warmed at 30 °C overnight and monitored by TLC. Then the solvent was evaporated under vacuum, and the crude solution was purified by column chromatography (petroleum ether/EtOAc, 4:1). The resulting product was identified as **3a**; yield 150 mg (43%); colorless oil; R_f = 0.56 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz): δ = 1.15–1.24 (m, 6 H, 2 $CO_2CH_2CH_3$), 1.26–1.30 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.83 (s, 3 H, CH_3), 3.08, 3.19 (AB, J = 15.6 Hz, 2 H, CH_2), 4.08–4.4.26 (m, 7 H, 3 $CO_2CH_2CH_3$, NH), 7.35–7.45 (m, 3 H, aryl), 7.82–7.85 (m, 2 H, aryl) ppm. ^{13}C NMR: δ = 13.76, 13.97, 14.02, 22.54, 43.36, 60.74, 61.92, 62.03, 91.93, 107.49, 128.50, 128.87, 129.42, 131.69, 167.88, 168.16, 169.61, 169.87 ppm. $C_{20}H_{26}N_2O_6$ (390.43): calcd. C 61.53, H 6.71, N 7.18; found C 61.32, H 6.88, N 7.04.

Diethyl 2-[2-(Ethoxycarbonyl)-1-oxo-1-phenylpropan-2-ylimino]succinate (3b): The product was obtained according to the procedure explained for **3a**; yield 50 mg (14%); colorless oil; R_f = 0.72 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (200 MHz): δ = 1.08–1.16 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.19–1.33 (m, J = 7.0 Hz, 6 H, 2 CH_2CH_3), 1.70 (s, 3 H, CH_3), 2.99, 3.56 (AB, J = 16.6 Hz, 2 H, CH_2), 4.13–4.31 (m, 6 H, 3 $CO_2CH_2CH_3$), 4.45 (br. s, 1 H, NH), 7.38–7.55 (m, 3 H, aryl), 7.92–7.96 (m, 2 H, aryl) ppm. ^{13}C NMR: δ = 13.73, 13.82, 13.93, 23.43, 42.49, 62.10, 62.42, 62.94, 79.37 128.40, 128.55, 129.38, 133.63, 151.73, 168.57, 169.21, 170.21, 195.83 ppm. MS (ESI): *m*/*z* = 392 [M + H]$^+$, 414 [M + Na]$^+$. $C_{20}H_{25}NO_7$ (391.42): calcd. C 61.37, H 6.44, N 3.58; found C 61.69, H 6.36, N 3.84.

Diethyl 5-Benzoyl-4,5-dihydro-5-methyl-4-oxo-1*H*-pyrrole-2,3-dicarboxylate (6): To a stirred solution of amino keto ester **5** (47 mg, 0.21 mmol) in diethyl ether (3.0 mL) was added DEAD (0.37 mL, 2.30 mmol). The reaction was warmed (30 °C) for 2 h. The presence of a white solid was observed, which was filtered and recrystallized (ethanol); yield 62 mg (85%); white crystals; m.p. 197–204 °C. ^{1}H NMR (200 MHz): δ = 1.27–1.34 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.37–1.44 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.82 (s, 3 H, CH_3), 4.23–4.34 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 4.40–4.52 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 7.81 (br. s, 1 H, NH), 7.40–7.61 (m, 3 H, aryl), 8.05–8.16 (m, 2 H, aryl) ppm. MS (ESI): *m*/*z* = 344 [M – H]$^-$, 368 [M + Na]$^+$. $C_{18}H_{19}NO_6$ (345,35): calcd. C 62.60, H 5.55, N 4.06; found C 62.85, H 5.27, N 4.12.

Dimethyl 2-(5-Methoxy-4-methyl-3-phenyl-1*H*-pyrazol-1-ylimino)-succinate (8): A solution of pyrazole **7a** (203 mg, 1.00 mmol) and DMAD (0.61 mL, 5.00 mmol) in diethyl ether (5.0 mL) was warmed (30 °C) and stirred overnight and monitored by TLC. The solvent was removed under vacuum, and the crude solution was purified by column chromatography (petroleum ether/EtOAc, 4:1) to give **8** as the first eluted fraction; yield 144 mg (42%); orange oil. ^{1}H NMR (400 MHz): δ = 2.15 (s, 3 H, CH_3), 3.60 (s, 3 H, OCH_3), 3.90 (s, 3 H, CO_2CH_3), 4.08 (s, 3 H, CO_2CH_3), 4.34 (s, 2 H, CH_2), 7.31–7.41 (m, 3 H, aryl), 7.67–7.69 (m, 2 H, aryl) ppm. ^{13}C NMR: δ = 8.45, 35.85, 51.99, 52.20, 53.38, 100.10, 127.23, 128.37, 131.19, 131.51, 133.37, 139.35, 152.20, 165.48, 169.03 ppm. MS (ESI): *m*/*z* = 346 [M + H]$^+$, 368 [M + Na]$^+$. $C_{17}H_{19}N_3O_5$ (345,35): calcd. C 59.12, H 5.55, N 12.17; found C 59.20, H 5.47, N 12.25.

Dimethyl 4-Hydroxy-4-methyl-5-phenyl-4*H*-pyrazolo[1,5-*b*]pyrazole-2,3-dicarboxylate (9): A solution of aminopyrazolone **7b** (90 mg, 0.50 mmol) and DMAD (0.31 mL, 2.50 mmol) in THF (5.0 mL) was stirred and warmed (40 °C) overnight. The solvent was then removed under vacuum, and the crude mixture was purified by LC by using a "Lobar LiChroprep 60" silica column and petroleum ether/ethyl acetate (1:1) as the mobile phase. After removal of the solvent, a yellow amorphous solid was obtained, to which was added methanol. The solvent was allowed to evaporate slowly to get a single crystal for X-ray diffraction analysis; yield 50 mg (30%); colorless crystal; m.p. 127–129 °C; R_f = 0.35 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz): δ = 1.86 (s, 3 H, CH_3), 3.87 (s, 3 H, CO_2CH_3), 3.88 (s, 3 H, CO_2CH_3), 4.40 (br. s, 1 H, OH), 7.40–7.53 (m, 3 H, aryl), 8.21 (d, 2 H, aryl) ppm. ^{13}C NMR: δ = 24.16, 52.45, 52.68, 80.81, 109.82, 127.57, 128.11, 128.72, 128.93, 132.53, 161.55, 162.13, 173.94 ppm. MS (ESI): *m*/*z* = 328 [M – H]$^-$, 330 [M + H]$^+$, 352 [M + Na]$^+$. $C_{16}H_{15}N_3O_5$ (329,31): calcd. C 58.36, H 4.59, N 12.76; found C 58.49, H 4.37, N 12.89.

Dimethyl 2-(1,5-Dimethyl-3-oxo-4-phenyl-1,3-dihydropyrazol-2-ylimino)succinate (11a): To a stirred solution of aminopyrazolone **10a** (69 mg, 0.34 mmol) in THF (4.0 mL) was added DMAD (0.21 mL, 1.70 mmol). The solution was warmed (40 °C) for 48 h and monitored by TLC. The solvent was then removed by evaporation under vacuum, and the residue was purified by column chromatography (petroleum ether/EtOAc, 1:1); yield 67 mg (57%); yellow oil; R_f = 0.61 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz): δ = 2.29 (s, 3 H, CH_3), 3.32 (s, 3 H, NCH_3), 3.67 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, CO_2CH_3), 3.92 (s, 2 H, CH_2), 7.22–7.38 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 12.09, 35.01, 37.12, 52.28, 53.26, 106.97, 126.84, 128.35, 128.46, 128.79, 152.06, 156.29, 165.00, 167.52, 168.35 ppm. MS (ESI): *m*/*z* = 346 [M + H]$^+$, 368 [M + Na]$^+$. $C_{17}H_{19}N_3O_5$ (345.35): calcd. C 59.12, H 5.55, N 12.17; found C 59.34, H 5.48, N 12.30.

Dimethyl 2-(1,4-Dimethyl-3-oxo-5-phenyl-1,3-dihydropyrazol-2-ylimino)succinate (11b): The reaction was performed as outlined for **11a** starting from **10b** (101 mg, 0.5 mmol), and the product was obtained from the crude solution by column chromatography (petroleum ether/EtOAc, 2:1); yield 135 mg (78%). ^{1}H NMR (400 MHz): δ = 1.81 (s, 3 H, CH_3), 2.96 (s, 3 H, NCH_3), 3.65 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, CO_2CH_3), 3.88 (s, 2 H, CH_2), 7.37–7.45 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 7.72, 36.98, 37.90, 52.13, 53.15, 104.26, 128.37, 128.81, 129.04, 130.25, 152.37, 158.29, 163.52, 164.05, 168.51 ppm. MS (ESI): *m*/*z* = 344 [M – H]$^-$, 346 [M + H]$^+$, 368 [M + Na]$^+$. $C_{17}H_{19}N_3O_5$ (345.35): calcd. C 59.12, H 5.55, N 12.17; found C 59.08, H 5.81, N 12.32.

Diethyl 2-(4,5-Dihydro-3-methyl-5-oxo-4-phenyl-1*H*-pyrazol-4-ylamino)maleate (13a): The product was obtained after chromatographic separation (petroleum ether/EtOAc, 2:1) of the crude solution of aminopyrazolone **12a** (0.5 mmol, 90 mg) and DEAD (2.5 mmol, 0.4 mL) warmed at 30 °C in diethyl ether (5.0 mL); yield 80 mg (45%); yellow oil. ^{1}H NMR (200 MHz): δ = 1.13–1.20 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.25–1.30 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 2.0 (s, 3 H, 3-Me), 3.97–4.08 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.18–4.28 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.44 (s, 1 H, NH), 5.46 (s, 1 H, CH), 7.33 (s, 5 H, aryl), 9.45 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.89, 14.32, 31.85, 60.00, 62.26, 70.56, 93.59, 125.42, 129.40, 129.67, 135.98, 148.35, 160.95, 163.51, 169.86 ppm. MS (ESI): *m*/*z*

= 360 [M + H]$^+$, 382 [M + Na]$^+$. $C_{18}H_{21}N_3O_5$ (359.38): calcd. C 60.16, H 5.89, N 11.69; found C 60.31, H 6.02, N 11.60.

Diethyl 4-Methyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (15a): The product was obtained after chromatographic separation (petroleum ether/EtOAc, 3:1) of the crude solution of aminopyrazolone **12a** (0.5 mmol, 90 mg) and DEAD (2.5 mmol, 0.4 mL) in diethyl ether (5.0 mL); yield 20 mg (13%); yellow needles; m.p. 75–78 °C; R_f = 0.94 (ethyl acetate/petroleum ether, 2:1). δ = 1.23–1.40 (t, J = 7.6 Hz, 6 H, 2 CH_2CH_3), 2.23 (s, 3 H, CH_3), 4.23–4.38 (q, J = 7.6 Hz, 4 H, 2 CH_2CH_3), 7.39–7.44 (m, 5H, Ph) ppm. ^{13}C NMR: δ = 10.70, 14.30, 29.70, 60.86, 60.94, 118.44, 120.37, 122.56, 127.56, 128.03, 128.89, 131.11, 132.94, 160.22, 165.83 ppm. MS (ESI): m/z = 300 [M – H]$^-$. GC–MS: m/z = 301 [M$^{\cdot}$]$^+$, 255 [M – 46$^{\cdot}$]$^+$. $C_{17}H_{19}NO_4$ (301.34): calcd. C 67.76, H 6.36, N 4.65; found C 67.59, H 6.16, N 4.80.

Diethyl 2-(4,5-Dihydro-4-methyl-5-oxo-3-phenyl-1*H*-pyrazol-4-ylamino)maleate (13b): The product was obtained after chromatographic separation (petroleum ether/EtOAc, 1:1) of the crude solution of aminopyrazolone **12b** (0.26 mmol, 50 mg) and DEAD (1.3 mmol, 0.21 mL) warmed at 45 °C in THF (5.0 mL); yield 69 mg (74%); yellow oil. ^{1}H NMR (200 MHz): δ = 1.14–1.21 (t, J = 6.7 Hz, 3 H, CH_2CH_3), 1.27–1.32 (t, J = 6.7 Hz, 3 H, CH_2CH_3), 1.62 (s, 3 H, 4-Me), 3.85–4.38 (m, J = 6.7 Hz, 2 H, CH_2CH_3), 5.86 (s, 1 H, CH), 7.30–7.48 (m, 3 H, aryl), 7.72–7.92 (m, 2 H, aryl), 8.71 (s, 1 H, NH), 9.28 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.66, 14.29, 26.29, 32.07, 59.98, 62.02, 93.24, 125.89, 128.82, 130.13, 147.47, 157.79, 162.00, 170.13, 176.23 ppm. MS (ESI): m/z = 360 [M + H]$^+$, 382 [M + Na]$^+$, 358 [M – H]$^-$. $C_{18}H_{21}N_3O_5$ (359.38): calcd. C 60.16, H 5.89, N 11.69; found C 60.03, H 5.75, N 11.82.

Diethyl 5-Methyl-4-phenyl-1*H*-pyrrole-2,3-dicarboxylate (15b): The product was obtained after chromatographic separation (petroleum ether/EtOAc, 1:1) of the crude solution of aminopyrazolone **12b** (0.26 mmol, 50 mg) and DEAD (1.3 mmol, 0.21 mL) warmed at 45 °C in THF (5.0 mL); yield 10 mg (13%). Melting point and NMR spectra were identical to those obtained with authentic sample.[2g]

Diethyl 2-(4,5-Dihydro-1,4-dimethyl-5-oxo-3-phenyl-1*H*-pyrazol-4-ylamino)maleate (13c): The purified product was obtained after chromatographic separation (petroleum ether/ethyl acetate, 3:1) of the crude solution of aminopyrazole **12c** (230 mg, 1.13 mmol) and DEAD (0.91 mL, 5.66 mmol) warmed at 30 °C in diethyl ether (20.0 mL); yield 244 mg (58%); light-brown oil; R_f = 0.72 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz) δ = 1.04–1.11 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.23–1.31 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.68 (s, 3 H, CH_3), 3.14 (s, 3 H, NCH_3), 3.95–4.12 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 4.16–4.30 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 5.40 (s, 1 H, CH), 7.31–7.34 (m, 3 H, aryl), 7.76–7.81 (m, 2 H, Ph), 8.70 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.66, 13.86, 14.29, 26.29, 32.07, 59.98, 62.02, 62.97, 63.31, 93.23, 125.89, 126.14, 126.65, 128.82, 129.47, 130.13, 147.47, 157.79, 170.13, 176.23 ppm. MS (ESI): m/z = 374 [M + H]$^+$, 396 [M + Na]$^+$, 412 [M + K]$^+$. $C_{19}H_{23}N_3O_5$ (373.40): calcd. C 61.11, H 6.21, N 11.25; found C 61.23, H 6.06, N 11.47.

Diethyl 1,2,3,3a,4,6a-Hexahydro-2,3a-dimethyl-3-oxo-6a-phenylpyrrolo[3,2-*c*]pyrazole-5,6-dicarboxylate (14c): The purified product was obtained after chromatographic separation (petroleum ether/ethyl acetate, 3:1) of the crude solution of aminopyrazole **12c** (230 mg, 1.13 mmol) and DEAD (0.91 mL, 5.66 mmol) warmed at 30 °C in diethyl ether (20.0 mL). Further purification was achieved through crystallization (chloroform); yield 105 mg (25%); white crystals; m.p. 204–206 °C; R_f = 0.49 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 0.91 (s, 3 H, CH_3), 1.00–1.08 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.31–1.39 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 3.14 (s, 3 H, NCH_3), 3.96–4.04 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 4.28–4.39 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.96 (s, 1 H, NH), 7.24–7.44 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 11.81, 14.00, 14.27, 17.56, 29.18, 31.02, 60.00, 60.74, 61.01, 62.42, 71.86, 74.89, 107.31, 117.92, 126.81, 127.89, 128.20, 128.42, 129.22, 137.54, 150.13, 161.73, 163.89, 167.86 ppm. MS (ESI): m/z = 372 [M – H]$^-$, 396 [M + H]$^+$, 769 [2M + Na]$^+$. $C_{19}H_{23}N_3O_5$ (373.40): calcd. C 61.11, H 6.21, N 11.25; found C 61.32, H 6.06, N 11.40.

Diethyl 2-(4,5-Dihydro-1,3-dimethyl-5-oxo-4-phenyl-1*H*-pyrazol-4-ylamino)maleate (13d): The purified product was obtained after chromatographic separation (petroleum ether/ethyl acetate, 3:1) of the crude solution of aminopyrazole **12d** (100 mg, 0.49 mmol) and DEAD (0.39 mL, 2.46 mmol) warmed at 30 °C in diethyl ether (10.0 mL); yield 158 mg (85%); yellow solid; m.p. 145–151 °C; R_f = 0.64 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (200 MHz) δ = 1.23–1.35 (m, J = 6.8 Hz, 6 H, 2 CH_2CH_3), 2.12 (s, 3 H, CH_3), 3.19 (s, 3 H, NCH_3), 4.11–4.19 (m, J = 6.8 Hz, 4 H, 2 CH_2CH_3), 5.49 (s, 1 H, CH), 7.32–7.46 (m, 5 H, aryl), 8.86 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.89, 14.20, 14.32, 31.85, 60.00, 62.26, 70.56, 93.59, 125.42, 129.40, 129.67, 135.98, 148.35, 160.95, 163.51, 169.86 ppm. MS (ESI): m/z = 374 [M + H]$^+$, 396 [M + H]$^+$, 412 [M + K]$^+$. $C_{19}H_{23}N_3O_5$ (373.40): calcd. C 61.11, H 6.21, N 11.25; found C 60.97, H 6.40, N 11.48.

Diethyl 1,2,3,3a,4,6a-Hexahydro-2,6a-dimethyl-3-oxo-3a-phenylpyrrolo[3,2-*c*]pyrazole-5,6-dicarboxylate (14d): The purified product was obtained after chromatographic separation (petroleum ether/ethyl acetate, 3:1) of the crude solution of aminopyrazole **12d** (100 mg, 0.49 mmol) and DEAD (0.39 mL, 2.46 mmol) warmed at 30 °C in diethyl ether (10.0 mL); yield 18 mg (10%); brown oil; R_f = 0.57 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (200 MHz): δ = 1.04 (s, 3 H, CH_3), 1.19–1.26 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.28–1.37 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 3.19 (s, 3 H, NCH_3), 4.12–4.23 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.26–4.36 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 5.33 (s, 1 H, NH), 7.25–7.37 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 2.78, 8.64, 10.70, 14.02, 14.15, 19.01, 19.51, 31.86, 40.96, 53.43, 60.27, 60.87, 62.36, 63.45, 73.35, 126.60, 127.57, 128.06, 128.92, 133.92, 147.85, 161.60, 163.81, 170.9 ppm. MS (ESI): m/z = 374 [M + H]$^+$, 396 [M + Na]$^+$, 372 [M – H]$^-$. $C_{19}H_{23}N_3O_5$ (373.40): calcd. C 61.11, H 6.21, N 11.25; found C 61.22, H 6.07, N 11.09.

Diethyl 2-(1-Benzyl-4,5-dihydro-3-methyl-5-oxo-4-phenyl-1*H*-pyrazol-4-ylamino)maleate (13e): The purified product was obtained after chromatographic separation (petroleum ether/ethyl acetate, 1:1) of the crude solution of aminopyrazole **12e** (178 mg, 0.64 mmol), and DEAD (0.51 mL, 3.2 mmol) warmed at 30 °C in diethyl ether (5.0 mL); yield 198 mg (69%); orange oil; R_f = 0.49 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 1.07–1.10 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.28–1.31 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 2.02 (s, 3 H, CH_3), 4.07–4.10 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.11–4.13 (t, J = 7.0 Hz, 2 H, CH_2CH_3), 4.48–4.52 (d, J = 15.1 Hz, 1 H, NCH_2Ph), 4.85–4.88 (d, J = 15.1 Hz, 1 H, NCH_2Ph), 7.15–7.35 (m, 5 H, aryl), 8.88 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.89, 14.07, 14.19, 48.32, 59.87, 62.01, 70.70, 93.57, 125.28, 127.33, 127.91, 128.28, 128.63, 129.06, 135.88, 136.28, 148.24, 160.97, 163.20, 169.72, 173.91 ppm. MS (ESI): m/z = 450 [M + H]$^+$, 472 [M + Na]$^+$. $C_{25}H_{27}N_3O_5$ (449.50): calcd. C 66.80, H 6.05, N 9.35; found C 67.01, H 6.11, N 9.28.

Diethyl 2-(4-Amino-4,5-dihydro-3-methyl-5-oxo-4-phenylpyrazol-1-yl)but-2-enedioate (16): To a stirred solution of aminopyrazolone **12a** (90 mg, 0.50 mmol) in THF (2.0 mL), was added triethylamine (0.14 mL, 1.0 mmol). After 15 min, DEAD (0.40 mL, 2.50 mmol)

was added to the solution. A sudden change in the color of the solution was observed. The solution was stirred overnight and monitored by TLC. The solvent from the crude solution was removed in vacuo, and the residue was purified by chromatography (petroleum ether/EtOAc, 1:1) to give **16**; yield 101 mg (56%); yellow oil; R_f = 0.70 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 1.19–1.26 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.27–1.34 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.89 (s, 3 H, CH_3), 4.12–4.22 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 4.25–4.35 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 6.83 (s, 1 H, CH), 7.24–7.52 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 12.81, 13.85, 13.90, 61.18, 62.44, 67.07, 124.27, 125.38, 128.49, 128.81, 134.47, 135.54, 162.20, 163.03, 163.17, 175.56 ppm. MS (ESI): m/z = 360 $[M + H]^+$, 382 $[M + Na]^+$. $C_{18}H_{21}N_3O_5$ (359.38): calcd. C 60.16, H 5.89, N 11.69; found C 60.42, H 5.68, N 11.87.

Diethyl 1-Acetyl-1,3a,6,6a-tetrahydro-6a-hydroxy-3a-methyl-3-phenylpyrrolo[3,2-*c*]pyrazole-5,6-dicarboxylate (21a): A solution of aminopyrazolone **20** (100 mg, 0.43 mmol) and DEAD (0.35 mL, 2.2 mmol) in dichloromethane (5.0 mL) was stirred and warmed up to 40 °C for 72 h. After that the solvent was removed under vacuum, and the crude solution was purified by column chromatography (petroleum ether/EtOAc, 1:1) to give **21a**; yield 106 mg (62%); colorless needles; m.p. 123–127 °C; R_f = 0.63 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 1.21–1.34 (m, 6 H, 2 CH_2CH_3), 1.60 (s, 3 H, CH_3), 2.38 (s, 3 H, $COCH_3$), 4.23–4.34 (m, 4 H, 2 CH_2CH_3), 4.68 (s, 1 H, CH), 5.16 (br. s, 1 H, OH), 7.40–7.44 (m, 3 H, aryl), 8.02–8.11 (m, 2 H, aryl) ppm. ^{13}C NMR: δ = 13.97, 14.10, 16.76, 21.88, 62.14, 62.50, 62.96, 63.34, 68.16, 96.42, 128.25, 128.61, 129.32, 130.50, 155.83, 160.79, 162.36, 165.94, 170.97 ppm. MS (ESI): m/z = 400 $[M - H]^-$, 402 $[M + H]^+$, 424 $[M + Na]^+$. $C_{20}H_{23}N_3O_6$ (401.41): calcd. C 59.84, H 5.78, N 10.47; found C 59.71, H 5.93, N 10.34.

Dimethyl 1-Acetyl-1,3a,6,6a-tetrahydro-6a-hydroxy-3a-methyl-3-phenylpyrrolo[3,2-*c*] pyrazole-5,6-dicarboxylate (21b): The reaction was performed as outlined for **21a** by using **20** (300 mg. 1.30 mmol) and DMAD (0.80 mL, 6.50 mmol) in dichloromethane (8.0 mL). After 72 h the solvent was removed in vacuo, and the presence of a white solid was noticed. A small quantity of diethyl ether was then added, and the white solid (**21b**) was filtered through a Buchner filter and characterized without further purification; yield 292 mg (60%); white powder; m.p. 190–193 °C; R_f = 0.61 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (200 MHz): δ = 1.61 (s, 3 H, CH_3), 2.38 (s, 3 H, $COCH_3$), 3.82 (s, 3 H, CO_2CH_3), 3.88 (s, 3 H, CO_2CH_3), 4.73 (s, 1 H, CH), 5.00 (br. s, 1 H, OH), 7.40–7.48 (m, 3 H, aryl), 7.97–8.08 (m, 2 H, aryl) ppm. ^{13}C NMR: δ = 16.76, 21.93, 53.15, 53.29, 63.14, 93.32, 96.35, 128.14, 128.25, 128.69, 129.24, 130.60, 161.38, 161.99, 166.58, 171.08 ppm. MS (ESI): m/z = 372 $[M - H]^-$, 396 $[M + Na]^+$. $C_{18}H_{19}N_3O_6$ (373.76): calcd. C 57.90, H 5.13, N 11.25; found C 58.06, H 5.01, N 11.53.

X-ray Crystallography: Single crystals were obtained by dissolving a few milligrams of powder in the solvents mentioned and allowing the solution to evaporate at room temperature. A "Siemens P4" four-circle diffractometer and a "OXFORD Xcalibur S" with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and the ω scan technique were used for data collections. The structure was solved by direct methods implemented in the SHELXS-97 program. The refinement was carried out by full-matrix anisotropic least-squares methods on F^2 for all reflections for non-hydrogen atoms by using the SHELXL-97 program. The crystallographic views reported above were elaborated with ORTEP (50% probability thermal ellipsoids).

CCDC-752424 (for **14c**), -752425 (for **6**), -752426 (for **15a**), -752427 (for **9**), -752428 (for **21b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

Supporting Information (see also the footnote on the first page of this article): Experimental characterization data for compounds **2**–**21**.

Acknowledgments

The work was financially supported by the University of Siena as a PAR Project 2007. The authors wish to thank the "Centro di Analisi e Determinazioni Strutturali" of the University of Siena for MS spectra and X-ray data collection and Dr. Serena Ferrini for helpful collaborations.

[1] a) Q. Ding, Z. Wang, J. Wu, *J. Org. Chem.* **2009**, *74*, 921–924; b) I. Iqbal, M. Imran, P. Langer, *Synthesis* **2009**, 2430–2434; c) K. Kawashima, M. Hiromoto, K. Hayashi, A. Kakehi, M. Shiro, M. Noguchi, *Tetrahedron Lett.* **2007**, *48*, 941–944; d) A. R. Katritzky, Y. Zhang, S. K. Singh, *Heterocycles* **2003**, *60*, 1225–1239; e) Z. Riedl, G. Hajòs, P. Kovér, G. Kollenz, *Arkivoc* **2003**, 62–68; f) D. Ramaiah, M. Muneer, K. R. Gopidas, P. K. Das, N. P. Rath, M. V. George, *J. Org. Chem.* **1996**, *61*, 4240–4246; g) A. Padwa, A. D. Woolhouse, J. J. Blount, *J. Org. Chem.* **1983**, *48*, 1069–1074.

[2] a) M. Anary-Abbasinejad, K. Charkhati, H. Anaraki-Ardakani, *Synlett* **2009**, 1115–1117; b) I. Erden, G. Olzer, C. Hoarau, W. Cao, J. Song, C. Gartner, I. Baumgardt, H. Butenschon, *J. Org. Chem.* **2008**, *73*, 6943–6945; c) M. L. Crawley, I. Goljer, D. J. Jenkins, J. F. Mehlmann, L. Nogle, R. Dooley, P. H. Mahaney, *Org. Lett.* **2006**, *8*, 5837–5840; d) H. Mastalerz, A. V. Gavai, B. Fink, C. Struzynski, J. Tarrant, G. D. Vite, T. W. Wong, G. Zhang, D. M. Vyas, *Can. J. Chem.* **2006**, *84*, 528–533; e) L. A. Evans, K. E. Griffiths, H. Guthmann, P. J. Murphy, *Tetrahedron Lett.* **2002**, *43*, 299–301; f) P. Kolar, M. Tisler, *Synth. Commun.* **1994**, *24*, 1887–1893; g) J. Barluenga, F. Palacios, V. Gotor, *Synthesis* **1975**, 642–643; h) J. B. Hendrickson, R. Rees, J. F. Templeton, *J. Am. Chem. Soc.* **1964**, *86*, 107–111.

[3] S. Baktharaman, R. Hili, A. K. Yudin, *Aldrichimica Acta* **2008**, *41*, 109–119.

[4] a) Q. Zhu, H. Jiang, J. Li, M. Zhang, X. Wang, C. Qi, *Tetrahedron* **2009**, *65*, 4604–4613; b) D. Zewge, C. Chen, C. Deer, P. G. Dormer, D. L. Hughes, *J. Org. Chem.* **2007**, *72*, 4276–4279; c) D. Ramaiah, H. Ashok, R. Barik, D. Venugopal, N. P. Rath, K. Bhattacharyya, P. K. Das, M. V. George, *J. Org. Chem.* **1992**, *57*, 6032–6037; d) W. E. Truce, D. G. Brady, *J. Org. Chem.* **1966**, *31*, 3543–3550.

[5] J. B. Hendrickson, R. Rees, J. F. Templeton, *J. Am. Chem. Soc.* **1964**, *86*, 107–111.

[6] a) D. Fancelli, J. Moll, M. Varrasi, R. Bravo, R. Artico, D. Berta, S. Bindi, A. Cameron, I. Candiani, P. Cappella, P. Carpinelli, W. Croci, B. Forte, M. L. Giorgini, P. Storici, R. Tonani, P. Zugnoni, P. Vianello, *J. Med. Chem.* **2006**, *49*, 7247–7251; b) Y. Wang, A. Benn, N. Flinn, T. Monk, M. Ramjee, J. Watts, M. Quibell, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1327–1331.

[7] A. M. Celli, S. Ferrini, F. Ponticelli, *Eur. J. Org. Chem.* **2006**, 3021–3025 and references cited therein.

[8] D. Yang, Y. L. Yan, B. Lui, *J. Org. Chem.* **2002**, *67*, 7429–7431.

[9] L. A. Carpino, *J. Am. Chem. Soc.* **1958**, *80*, 599–601.

Received: March 17, 2010
Published Online: May 26, 2010

