Tetrahedron Letters 49 (2008) 6768–6772

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Lewis acid- and/or Lewis base-catalyzed [3+2] cycloaddition reaction: synthesis of pyrazoles and pyrazolines

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ARTICLE INFO

Article history:
Received 1 July 2008
Revised 2 September 2008
Accepted 7 September 2008
Available online 11 September 2008

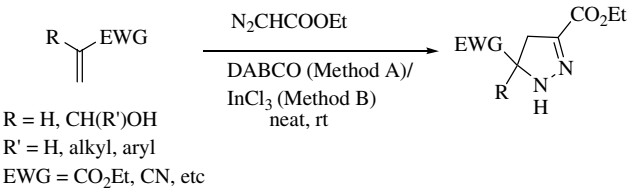
Keywords:
Ethyl diazoacetate
DABCO
Indium trichloride
Activated olefins
Baylis–Hillman adducts
Pyrazolines
Pyrazoles

ABSTRACT

A facile, $InCl_3$ and/or DABCO mediated 1, 3-dipolar cycloaddition of ethyl diazoacetate (EDA) with various activated olefins under solvent-free conditions at ambient temperature to afford 3, 5-disubstituted pyrazolines and pyrazoles in moderate to good yields is reported.

A large number of nitrogen-containing heterocyclic natural products possesses pharmacological activities.[1] Hence, formation of azaheterocycles continues to attract the attention of organic chemists. The most accessible routes are either (a) cyclization, which proceeds stepwise through one or more intermediates involving the expulsion of a small molecule such as an alcohol or water or (b) cycloaddition, which proceeds via no distinct intermediate but the bond formations may be asynchronous. Alternatively, a [3+2] cycloaddition reaction strategy to form five-membered ring systems through the reaction of 1,3-dipoles and dipolarophiles is an attractive protocol.[2] In continuation of our efforts in the development of various aspects of Baylis–Hillman reaction,[3] and the utility of the adducts thereof in organic synthesis,[3] herein, we report the use of Baylis–Hillman adducts for C–N bond formation[5] to result in heterocyclic ring formation affording pyrazolines (Scheme 1).

Pyrazoles[6] and pyrazolines[7] are widely used in agrochemistry as insecticides, and in pharmaceuticals for varied applications. In general, pyrazolines have been synthesized[8] by cycloaddition of nitrile imines,[9] 1,2-disubstituted (–COOR) alkene[10] and azides.[11] Though cycloaddition of diazoesters with activated olefins is known,[12] its versatility remains unexplored. Similarly, base-catalyzed cycloaddition reactions between EDA and activated olefins



Scheme 1. Cycloaddition between various olefins and ethyl diazoacetate.

were earlier reported[13] albeit under drastic reaction conditions. Interestingly, it may be noted that Baylis–Hillman adducts have been less studied as substrates in cycloaddition reactions.[14b] Toward this endeavor, herein, we report our results on the Lewis acid/Lewis base-catalyzed cycloaddition of various acrylates, including Baylis–Hillman adducts as dipolarophiles with ethyl diazoacetate (dipole) to afford the corresponding pyrazolines. Synthesis of various pyrazoles from commercially available alkynes and EDA under similar reaction conditions is also reported.

With the aim of identifying mild reaction conditions for the [3+2] cycloaddition reaction involving EDA, to encompass all kinds of olefins, we undertook a study on the Lewis acid/Lewis base-mediated synthetic protocol. The initial reaction contemplated was between ethyl acrylate **1** and ethyl diazoacetate (EDA) in order to obtain **5** as the lone product in good yields. During the study, we found that DABCO and $InCl_3$ effectively catalyze the cycloaddition to afford **5** in 97% and 80% yields, respectively, in 2 h at ambient

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doi:10.1016/j.tetlet.2008.09.037

Table 1
Optimization of reaction conditions for cycloaddition reaction between ethyl acrylate **1** and ethyl diazoacetate

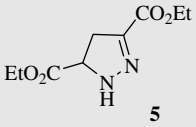
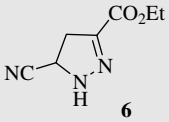
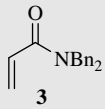
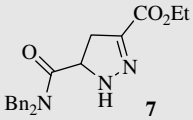
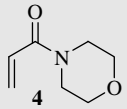
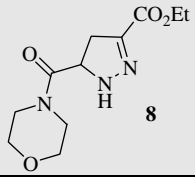
Entry	Lewis acid/Lewis base	Solvent	Time (h)	Product[a,b] (%)
1	DABCO	THF	24	0
2	DABCO	DCM	24	25
3	DABCO	DMF	10	82
4	DABCO	Dioxane/H_2O	6	90
5[c]	DABCO	Neat	2	97
6	DBU	Neat	2	0
7	HMTA	Neat	4	89
8	NMM	Neat	5	83
9	$BF_3{\cdot}OEt_2$	Neat	4	45
10	$FeCl_3$	Neat	5	61
11[c]	$InCl_3$	neat	2	80
12	No catalyst	Neat	24	0

[a] Determined by ^1H NMR of pure compound.
[b] Isolated yields after column chromatography.
[c] The best yield under these conditions.

temperature. The DABCO-catalyzed reaction was standardized using various solvents such as dichloromethane, THF, DMF, and aq 1,4-dioxane (Table 1, entries 1–4). Of all the solvents studied, aq 1,4-dioxane gave **5** in high yield (90%) but in 6 h. The same reaction under solvent-free conditions afforded **5** in excellent yield (97%) in a shorter time (Table 1, entry 5). A blank reaction (Table 1, entry 12) did not result in any product, thus proving the role of the catalysts.

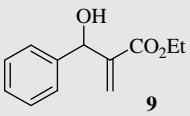
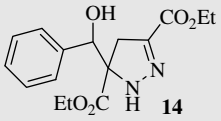
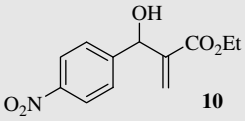
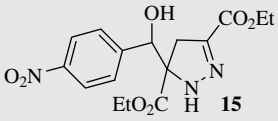
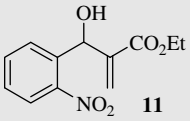
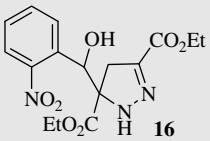
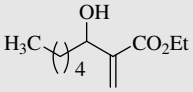
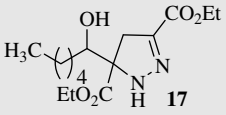
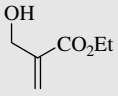
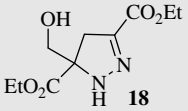
Simultaneously, the effects of different Lewis acid/and bases for the [3+2] cycloaddition reaction were also examined (Table 1, entries 6–11). Among the various Lewis bases that were examined, DABCO (Table 1, entry 5) provided **5** in the best yield under solvent-free conditions when compared to NMM (Table 1, entry 8) and hexamethylenetetramine (HMTA, Table 1, entry 7). Surpris-

Table 2
Cycloaddition between electron poor olefins and ethyl diazoacetate under methods A/B

Entry	Dipolarophile	Product[a]	Method[b]	Time (h)	Yield[c] (%)
1	 **1**	 **5**	A	2	97
			B	4	80
2	 **2**	 **6**	A	6	52
			B	10	46
3[d]	 **3**	 **7**	A	4	69
			B	8	56
4	 **4**	 **8**	A	5	58
			B	7	49

[a] All the products were characterized by their spectral data.
[b] *Method A:* Olefin (1.0 equiv), EDA (1.0 equiv), and DABCO (0.1 equiv) were stirred at ambient temperature for the specified time to afford the products after purification. *Method B*: Olefin (1.0 equiv), EDA (1.0 equiv), and $InCl_3$ (0.1 equiv) were stirred at ambient temperature until the completion of the reaction.
[c] Isolated yields.
[d] For these substrates, olefin and EDA were taken in a 2:1 ratio with the catalyst (0.1 equiv).

Table 3
Cycloaddition between various Baylis–Hillman adducts (dipolarophile) and ethyl diazoacetate under methods A/B

Entry	Dipolarophile	Product[a]	Method[b]	Time (h)	Yield[c] (%)
1	 **9**	 **14**	A	6	75
			B	8	60
2	 **10**	 **15**	A	2	95
			B	5	78
3	 **11**	 **16**	A	2	86
			B	5	66
4	 **12**	 **17**	A	3	85
			B	7	61
5	 **13**	 **18**	A	4	82
			B	7	71

[a] All the products were characterized by their spectral data.
[b] *Method A*: Olefin (1.0 equiv), EDA (1.0 equiv), and DABCO (0.1 equiv) were stirred at ambient temperature for the specified time to afford the products after purification. *Method B*: Olefin (1.0 equiv), EDA (1.0 equiv), and $InCl_3$ (0.1 equiv) were stirred at ambient temperature until the completion of the reaction.
[c] Isolated yields.

ingly, DBU (Table 1, entry 6) did not catalyze the [3+2] cycloaddition reaction. Amongst the Lewis acids, the indium chloride-catalyzed reaction afforded the desired product **5** in best yield (Table 1, 11) under solvent-free conditions (Table 1, entries 9 and 10). The study illustrated that the product yield increased with decreasing acidity of Lewis acids (Table 1, entries 9–11). Thus, between the two chosen catalysts, DABCO and $InCl_3$, the reaction was more facile with DABCO.

Pyrazoline **5** was characterized through its spectral data. For instance, its ^{1}H NMR spectrum revealed a characteristic signal for H-5 at δ 4.40 ppm (dd, J = 6.0, 12.8 Hz) and for H-4 at δ 3.30 ppm (ddd, J = 1.5, 5.8, 18.8 Hz) and δ 3.17 ppm (dd, J = 12.6, 18.8 Hz). The IR spectrum displayed the characteristic 1571 cm^{-1} for C–N stretching, apart from peaks due to other functional groups.

Encouraged by these preliminary results, we extended the scope of this cycloaddition reaction to several simple electron-poor olefins such as acrylonitrile **2** (Table 2, entry 2), *N*,*N*-dibenzyl acrylamide **3** (Table 2, entry 3), and 4-acryloylmorpholine **4** (Table 2, entry 4) with EDA to afford the corresponding pyrazolines (**6–8**) in moderate to good yields employing both Method A and Method B. The moderate yields of **6** may be explained due to the competing self-coupling reaction of acrylonitrile.[14a] Interestingly, the less reactive amides **3** and **4** afforded products in reasonable yields. As suggested by the referee,[15] the dual activation mode of both DABCO and $InCl_3$ was evaluated but without any clear advantage. The counter catalytic deactivation or synergistic activation of Lewis base in presence of Lewis acid or *vice versa* was not significant, and afforded comparable yields of the product (~85%) albeit in less time (1.5 h). Further, the reaction of EDA with 1,2-disubstituted dipolarophiles like (*E*)-ethyl crotonate and ethyl sorbate was also investigated. However, the reaction did not give the desired adducts unlike our earlier experiences.[4b]

The scope of the cycloaddition was further investigated with Baylis–Hillman adducts and EDA (Table 3). For instance, adduct **9** (Table 3, entry 1) underwent facile cycloaddition with EDA in presence of DABCO (Method A) as well as with $InCl_3$ (Method B) to afford pyrazoline **14** in 75% and 60% yields, respectively, under solvent-free conditions. Other adducts, such as the one with an electron-withdrawing substituent (p-NO_2 group) on the benzene ring (Table 3, entry 2), yielded the desired product **15** in excellent yield (95%), while the one possessing an o-NO_2 group (Table 3, entry 3) led to comparatively lower yield (86%) of the corresponding product **16** under similar reaction conditions. Adduct **12** possessing a long carbon chain (Table 3, entry 4) and the simplest adduct **13** (Table 3, entry 5) also provided the corresponding pyrazolines **17** and **18** in good yields. All the products were identified by their spectral data (Ref. 21). For instance, the ^{1}H NMR spectra of pyrazolines **5–8** revealed H-5 resonating from δ 4.5 to δ 4.2 ppm, while densely substituted pyrazolines **14–18** revealed H-4 ranging from δ 3.03 to 3.18 ppm**.** The regiochemistry of the products was assigned based on the literature precedents[12,13] as well as from the plausible mechanism (Fig. 1).

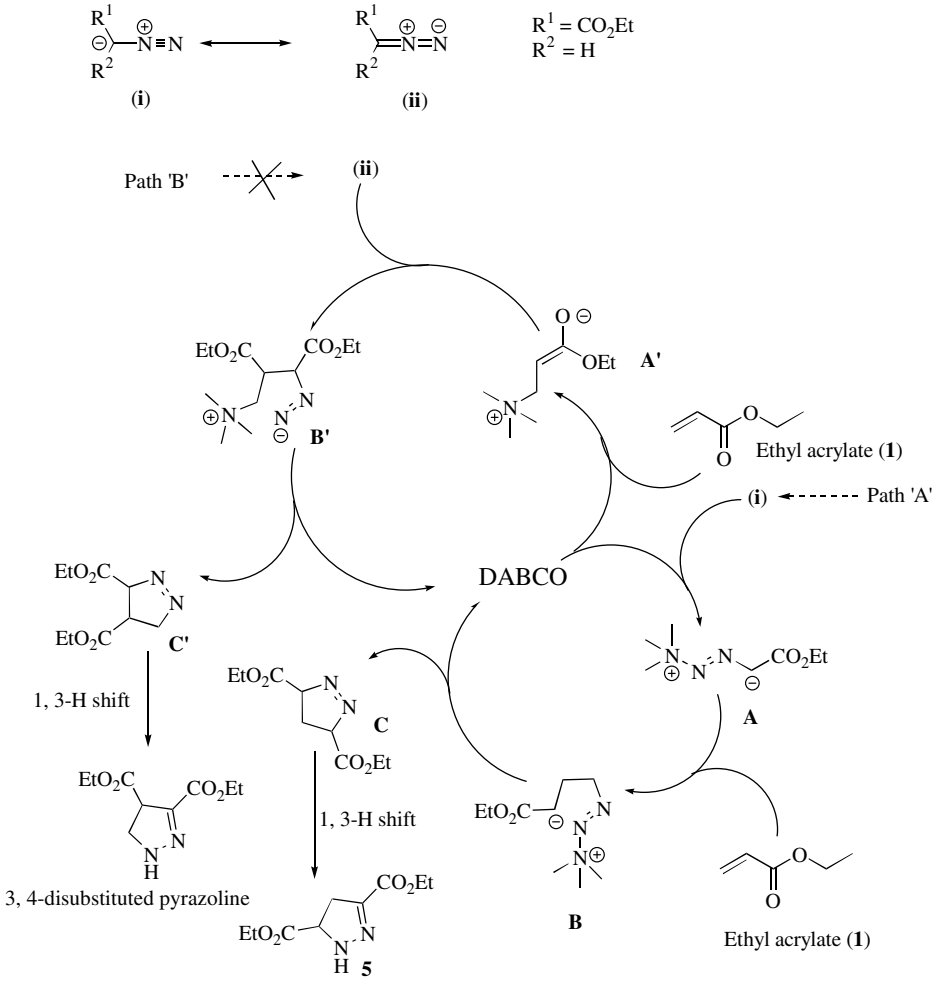
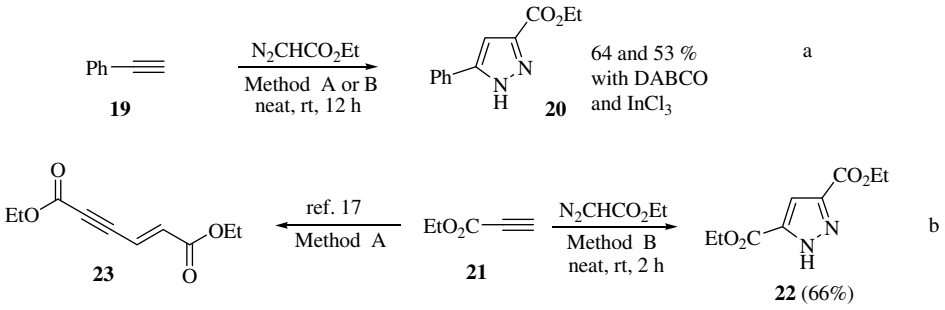


Figure 1. Plausible mechanism.



Scheme 2. Reaction of phenylacetylene and ethyl propiolate with ethyl diazoacetate under methods A and/or B conditions.

Interestingly, when the [3+2] cycloaddition was performed on simple alkynes such as phenylacetylene **19** and electron-poor alkyne ethyl propiolate **21,** both gave the corresponding pyrazoles **20** and **22** in moderate to good yields. The earlier reported method did not give the desired products under the Lewis acid conditions in aqueous medium.[16] Herein, while **19** gave **20** under both the reaction conditions (Methods A and B, Scheme 2, route a) in comparable yields, **21** gave the desired product **22** (Scheme 2, route b) in the presence of Lewis acid ($InCl_3$) alone, and underwent a facile self coupling reaction to give the undesired diethyl-2*E*-en-4-yn-1,6-dioate[17] (**23**) under Method A conditions as the only product (Scheme 2, route b). The ^1H NMR spectrum of **20** and **22** revealed the lone aromatic proton at δ 7.08 ppm and at δ 7.27 ppm, respectively. Though, the regiochemical disposition of the substituents in **20** cannot be conclusively proved through its spectral data at this point of time, we believe the cycloaddition reaction follows a pathway similar to that followed by other substrates.

The formation of the products can be explained based on the plausible mechanism as depicted in Figure 1. Thus, while the Lewis acid-catalyzed cycloaddition followed the standard reaction pathway,[18] the attack of Lewis base (DABCO) promoted activation of EDA presumably occurs to generate 'triazene intermediate'[19a] **A** (Pathway A, Fig. 1), which later undergoes Michael addition on electron-poor olefin (**1**) to result in adduct '**B**' followed by its ring-closure with simultaneous release of the Lewis base (DABCO) giving '**C**'. Intermediate '**C**' then undergoes a 1, 3-H shift forming a more stable, desired product (**5**). In an effort to understand the role of DABCO in the cycloaddition reaction, an experiment between DABCO and EDA was conducted. Even though the proposed intermediate **A** could not be detected from the NMR studies,[19b] we believe that it maybe the most likely intermediate.

On the other hand, the alternative pathway 'B' explains the formation of regioisomeric products (3, 4-disubstituted pyrazolines) through the Michael addition of DABCO on the olefin as the first step (Baylis–Hillman type mechanism), followed by the concurrent steps. The Pathway B is discounted, since the products obtained are different to those described in the present protocol.

In conclusion, a simple, general one-pot protocol for the synthesis of heterocyclic 3, 5-disubstituted pyrazolines and pyrazoles[20,21] was developed from different type of electron-poor olefins/alkynes including Baylis–Hillman adducts and EDA under mild conditions in good to excellent yields. Alkynes also provided the desired products. A variety of Lewis bases such as hexamethylenetetramine (HMTA), NMM, and DBU and Lewis acids like $BF_3{\cdot}OEt_2$, $FeCl_3$ apart from DABCO and $InCl_3$ were also screened during the standardization of cycloaddition reaction.

Acknowledgment

One of the authors (E.R.S.) thanks the CSIR, New Delhi, India, for financial support in the form of a fellowship.

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15. The authors are thankful to the referee who suggested the cylcoaddition experiments with either (*E*)- and (*Z*)-ethyl crotonate or fumarate, and to test whether any dual activation mode existed when DABCO and $InCl_3$ were used together.
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19. (a) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805–816; (b) Upon referee's suggestion, attempts were made to detect the formation of condensation product **A** by NMR studies. At this point of time, we do not have any evidence for the triazene-like intermediate **A**.
20. *General experimental procedure: Method A:* Activated olefin, ethyl acrylate **1** (0.1 g, 1 mmol), ethyl diazoacetate (0.114 g, 1.0 mmol), and DABCO (0.011 g, 0.1 mmol) were stirred for 2 h at ambient temperature until completion of reaction (tlc). The reaction mixture was purified by column chromatography (Silica gel, 60–120 mesh, EtOAC/hexane, 2:8) to afford pure **5** in 97% yield. *Method B*: A mixture of activated olefin, ethyl acrylate **1** (0.1 g, 1 mmol), ethyl diazoacetate (0.114 g, 1.0 mmol), and $InCl_3$ (0.022 g, 0.1 mmol) were stirred at ambient temperature for 4 h. The mixture was purified by column chromatography to afford **5** in 80% yield.
21. *Spectral data for selected compounds*: Compound **5**: Yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ 6.72 (br s, 1H, NH), 4.40 (dd, 1H, J = 6.0, 12.8 Hz, H-5), 4.34–4.15 (m, 4H, 2 × –OCH_2), 3.30 (ddd, 1H, J = 1.5, 5.8, 18.8 Hz, H-4), 3.17 (dd, 1H, J = 12.6, 18.8 Hz, H-4′), 1.50-1.20 (m, 6H, 2 × CH_3); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 171.5, 142.6, 61.9, 61.4, 34.6, 14.1; IR (neat): 3356, 2984, 1734, 1571, 1250 cm^{-1}; ES-MS: *m/z* = 214 (M^+). Anal. Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59. Found C, 50.41; H, 6.62. Compound **7**: Syrup; ^1H NMR (200 MHz, $CDCl_3$): δ 7.40–7.10 (m, 10H, Ar–H), 6.40 (br s, 1H, NH), 4.84 (d, *J* = 5.3 Hz, 2H, $-CH_2Ph$), 4.56 (d, *J* = 6.4 Hz, 2H, $-CH_2Ph$), 4.22 (dd, 1H, *J* = 5.2, 12.4 Hz, H-5), 4.20 (q, *J* = 6.7 Hz, 2H, $-OCH_2$), 3.49–3.25 (m, 2H, CH_2), 1.29 (t, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7, 146.6, 136.3, 128.0, 127.8, 127.5, 127.0, 126.8, 61.3, 59.3, 50.2, 47.7, 37.1, 13.5; IR (neat): 3348, 2925, 1735, 1622, 1449, 1239 cm^{-1}; ESI-MS: *m/z* = 338 (M^++1). Anal. Calcd. for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87. Found: C, 71.13; H, 6.93. Compound **8**: Syrup; ^1H NMR (200 MHz, $CDCl_3$): δ 6.81 (br s, 1H, NH), 4.51 (t, 1H, *J* = 5.2 Hz, H-5), 4.25 (q, 2H, *J* = 7.4 Hz, OCH_2), 3.70–3.54 (m, 6H, CH_2), 3.51–3.44 (m, 2H, CH_2), 3.28 (dd, 1H, *J* = 12.6, 17.0 Hz, CH_2), 3.01 (dd, 1H, *J* = 5.2, 17.0 Hz, CH_2), 1.40–1.18 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 161.8, 142.3, 66.5, 66.0, 61.2, 59.4, 45.5, 42.5, 36.2, 14.2. ESI-MS: *m/z* = 256 [M^++1]. Anal. Calcd. for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71. Found: C, 51.71; H, 6.78. Compound **14**: Syrup; ^1H NMR (200 MHz, $CDCl_3$): δ 7.31 (s, 5H, Ar–H), 6.81 (br s, 1H, NH), 4.99 (s, 1H, –CHOH), 4.30–4.10 (m, 4H, 2 × OCH_2), 3.18 (d, *J* = 2.5 Hz, 2H, H-4), 1.40–1.15 (m, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 143.2, 137.3, 126.6, 127.9, 75.1, 61.8, 60.8, 35.3, 29.2, 13.7, 13.4; IR (neat): 3448, 2984, 1731, 1638, 1253 cm^{-1}; ESI-MS: *m/z* = 343 [M^++23]. Anal. Calcd. for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29. Found: C, 60.04; H, 6.22. Compound **16**: Syrup; ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.8 Hz, 2H, Ar–H), 7.61 (t, *J* = 8.6 Hz, 1H Ar–H), 7.51 (t, *J* = 7.8 Hz, 1H, Ar–H), 7.10 (s, 1H, NH), 5.81 (s, 1H, –CHOH), 4.19 (m, 4H, 2 × CH_2), 3.10 (d, *J* = 3.4 Hz, 2H, H-4), 1.22 (m, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 148.7, 143.7, 133.5, 130.2, 129.2, 124.3, 68.9, 62.8, 61.4, 61.3, 59.8, 14.1, 13.8; IR (neat): 3449, 2924, 1727, 1636, 1256 cm^{-1}; ESI-MS: *m/z* = 388 [M^++23]. Anal. Calcd. for $C_{16}H_{19}N_3O_7$: C, 52.60; H, 5.24. Found: C, 52.65; H, 5.22%. Compound **17**: Syrup; ^1H NMR (300 MHz, $CDCl_3$): δ 6.63 (br s, 1H, NH), 4.31–4.02 (m, 5H, 1H, –CH–OH, 2 × CH_2), 3.41–2.98 (m, 2H, H-4), 1.45–1.23 (m, 14H), 0.92–0.85 (m, 3H, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 171.1, 161.8, 138.3, 64.3, 61.5, 36.8, 34.6, 31.2, 29.0, 25.0, 22.2, 13.7; IR (neat): 3354, 2980, 2934, 2867, 1739, 1703, 1252 cm^{-1}; ESI-MS: *m/z* = 296 (M^++23). Compound **18**: Syrup; ^1H NMR (200 MHz, $CDCl_3$): δ 4.29–4.14 (m, 4H, CH_2), 3.80 (d, 1H, *J* = 10.5 Hz, $-CH_2OH$), 3.60 (d, 1H, *J* = 10.5 Hz, $-CH_2OH$), 3.19 (d, 1H, *J* = 17.2 Hz, H-4), 2.88 (d, 1H, *J* = 17.2 Hz, H-4), 1.32 (2t, 6H, *J* = 4.5 and 7.5 Hz, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 161.7, 142.9, 73.8, 70.3, 65.1, 62.8, 62.2, 37.2, 14.0. ESI-MS: 245 [M^++1]. Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.60. Found: 49.24; H, 6.56. Compound **20**: Syrup; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 6.7 Hz, Ar–H), 7.43–7.30 (m, 3H, Ar–H), 7.08 (s, 1H, Ar–H), 4.37 (q, 2H, *J* = 6.7 Hz, CH_2), 1.41 (t, 3H, *J* = 6.7 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 130.8, 128.9, 128.5, 127.7, 125.7, 113.9, 105.6, 61.3, 14.2. IR (neat): 2924, 1724, 1244 cm^{-1}. ESI-MS: 217 [M^++1]. Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C, 66.69; H, 5.54. Compound **22**: Syrup; ^1H NMR (300 MHz, $CDCl_3$): δ 12.9 (br s, 1H, NH), 7.27 (s, 1H, Ar–H), 4.37 (q, 4H, *J* = 6.7 Hz, CH_2), 1.38 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 140.1, 111.2, 61.6, 14.1. IR (neat): 3145, 2984, 1729, 1250 cm^{-1}. ESI-MS: 213 [M^++1]. Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70. Found: C, 50.99; H, 5.67.