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Synthesis of new aza-bicyclic 2-isoxazolines by 1,3-dipolar cycloaddition of endocyclic enecarbamates and enamides with nitrile oxides

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ABSTRACT

Novel aza-bicyclic 2-isoxazolines, 4,5-dihydroisoxazole[5,4-*b*]pyrrolidines, and 4,5-dihydroisoxazole[5,4-*b*]piperidines were synthesized in a highly regioselective manner through a 1,3-dipolar cycloaddition reaction of 5- and 6-membered endocyclic enecarbamates and enamides with several nitrile oxides in good to excellent yields. Hydrogenolysis of 5- and 6-membered Cbz-cycloadducts led to secondary amines, which presented distinctive stabilities. 2-Isoxazoline bisamides were obtained in good yields through a N-benzoylation, followed by ammonolysis of the secondary amine, or directly from ammonolysis of the cycloadducts.

Endocyclic enecarbamates and enamides possess a strategically located enamine functionality which makes these nitrogen containing heterocycles very versatile precursors of other N-heterocycles and alkaloids.[1]

The [2+2] and [4+2] cycloaddition reactions involving enecarbamates and enamides have been reported before,[2,3] however, the 1,3-dipolar cycloaddition reactions involving these N-heterocycles have remained unreported in literature in spite of their potential as dipolarophiles. 1,3-Dipolar cycloaddition of endocyclic enecarbamate and enamide with nitrile oxides opens new routes to novel heterobicyclic compounds by incorporating the 2-isoxazoline nucleus.[4] Many compounds bearing the 2-isoxazoline nucleus show relevant biological activity, for instance, the glutamic acid antagonist (**1**), the antithrombotic (**2**), the antitumoral (**3**), the anti-inflammatory (**4**), among others (Fig. 1).[5–8] New transformations involving endocyclic enecarbamates and enamides have been the main focus of our research laboratories and herein we report on the development of a new synthetic methodology involving the 1,3-dipolar cycloaddition of endocyclic enecarbamates and enamides with nitrile oxides for the construction of new aza-bicyclic 2-isoxazolines: 4,5-dihydroisoxazole[5,4-*b*]pyrrolidines and 4,5-dihydroisoxazole[5,4-*b*]piperidines.

The 5-membered endocyclic enecarbamates and enamides (**8**) were prepared by direct application of the Kraus method,[9] whereas the 6-membered ones (**6**) were prepared using a modification of this methodology (Scheme 1).[10] Application of the Kraus method to the synthesis of 6-membered enecarbamates and enamides led to very low yields of the desired products (<10%).

Five different 1,3-dipoles (*p*-chlorobenzonitrile oxide, *p*-methoxybenzonitrile oxide, *p*-toluyilformonitrile oxide, (2-furfuryl)-formonitrile oxide, and carboethoxyformonitrile oxide-CEFNO) were tested in these 1,3-dipolar cycloaddition reactions with several endocyclic enecarbamates and enamides. CEFNO was formed in situ from ethyl chlorooximidoacetate, which was obtained from glycine ethyl ester hydrochloride,[11] while benzonitrile and other formonitrile oxides were formed in situ from the respective hydroximinoyl chloride precursors,[12] which in turn were obtained from the respective oximes (Schemes 1 and 2).[13]

When the pure ethyl chlorooximidoacetate was used as precursor to generate the CEFNO, the optimum condition for the 1,3-dipolar cycloaddition reactions, which provided the best output, such as low formation of CEFNO dimer, was the following: enecarbamate/enamide as limiting reagent, dry $CHCl_3$ or THF as solvent, dry Et_3N as base, slow addition of the CEFNO precursor into a solution of enamide/enecarbamate and Et_3N, at room temperature, under vigorous stirring.[14]

For the other nitrile oxides (benzonitrile oxides and (2-furfuryl)-formonitrile oxide), obtained in situ from their respective

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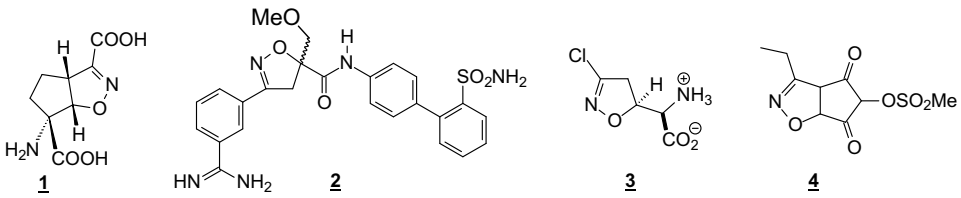
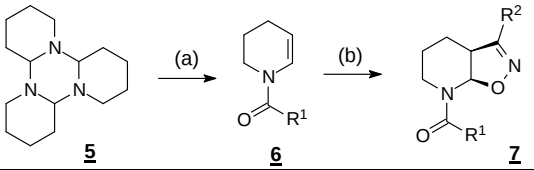


Figure 1. Some bioactive 2-isoxazolines.

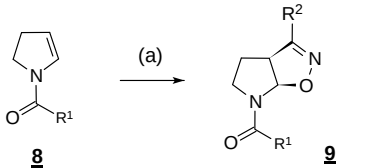
crude precursors, excess enecarbamates/enamides in dry $CHCl_3$, provided the best reaction condition, in which the dimer of the nitrile oxide is not observed.[14] The use of (2-furfuryl)-hydroximinoyl chloride, precursor of the (2-furfuryl)-formonitrile oxide, resulted in very low yields of the cycloadducts (**7l**) and (**9j**), probably due to its instability.

5-Membered endocyclic enecarbamates and enamides (**8**) underwent smooth 1,3-cycloaddition when CEFNO was used (Scheme 2). Complete conversion of the starting enecarbamate/enamide was observed in all cases evaluated, whereas 6-membered enecarbamates/enamides led to incomplete conversions with this reagent.



entry	enecarbamate / enamide (yield)	R^1	Cycloadducts (yield)	R^1	R^2
1	**6a** (90 %)	OEt	**7a** (70%)	OEt	COOEt
2	**6b** (94%)	OBn	**7b** (68%)	OBn	COOEt
3	**6c** (75%)	4-$NO_2C_6H_4$	**7c** (45%)	4-$NO_2C_6H_6$	COOEt
4	**6d** (95%)	4-FC_6H_4	**7d** (61%)	4-FC_6H_6	COOEt
5	**6e** (96%)	4-$OMeC_6H_4$	**7e** (64%)	4-$OMeC_6H_6$	COOEt
6	**6f** (94%)	4-$^tBuC_6H_4$	**7f** (60%)	4-$^tBuC_6H_6$	COOEt
7	**6g** (95%)	4-ClC_6H_4	**7g** (60%)	4-ClC_6H_6	COOEt
8	**6h** (95%)	4-BrC_6H_4	**7h** (55%)	4-BrC_6H_6	COOEt
9	**6i** (94%)	4-$CH_3C_6H_4$	**7i** (60%)	4-$CH_3C_6H_6$	COOEt
10	**6a**	OEt	**7j** (54%)	OEt	4-$OMeC_6H_4$
11	**6b**	OBn	**7k** (58%)	OBn	4-$CH_3C_6H_4$
12	**6f**	4-$^tBuC_6H_4$	**7l** (24%)[i]	4-$^tBuC_6H_4$	2-furfuryl
13	**6f**	4-$^tBuC_6H_4$	**7m** (62%)	4-$^tBuC_6H_4$	4-ClC_6H_4
14	**6e**	4-$OMeC_6H_4$	**7n** (64%)	4-$OMeC_6H_4$	4-ClC_6H_4

Scheme 1. Synthesis and 1,3-dipolar cycloaddition of 6-membered endocyclic enecarbamates and enamides (**6**). (a) Alkyl chloroformates or *p*-(R^1)-benzoyl chlorides, Et_3N, THF, reflux, (b) ethyl chlorooxiimidoacetate or benzohydroximinoyl chlorides or (2-furfuryl)-hydroximinoyl chloride [(i)]unstable, Et_3N, $CHCl_3$, or THF, rt.



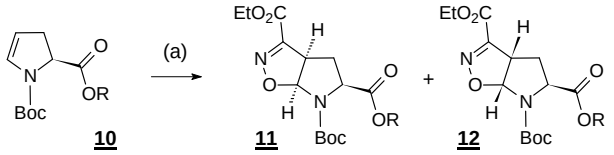
entry	Cycloadducts (yield)	R^1	R^2
1	**9a** (80%)	OEt	COOEt
2	**9b** (78%)	OBn	COOEt
3	**9c** (64%)	4-$NO_2C_6H_4$	COOEt
4	**9d** (70%)	4-FC_6H_4	COOEt
5	**9e** (75%)	4-$OMeC_6H_4$	COOEt
6	**9f** (74%)	4-$^tBuC_6H_4$	COOEt
7	**9g** (65%)	4-ClC_6H_4	COOEt
8	**9h** (68%)	4-$^tBuC_6H_4$	4-ClC_6H_4
9	**9i** (60%)	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$
10	**9j** (29%)[i]	4-$^tBuC_6H_4$	2-furfuryl
11	**9k** (70%)	OBn	4-$OMeC_6H_4$
12	**9l** (72%)	OEt	4-ClC_6H_4

Scheme 2. 1,3-Dipolar cycloaddition of 5-membered endocyclic enecarbamates/enamides (**8**). (a) Ethyl chlorooxiimidoacetate or benzohydroximinoyl chlorides or (2-furfuryl)-hydroximinoyl chloride [(i)]unstable, Et_3N, $CHCl_3$, or THF, rt.

The chiral 5-membered endocyclic enecarbamates (**10**) were prepared as described before[15] and were submitted to the 1,3-dipolar cycloaddition with CEFNO (Scheme 3) applying the same optimized reaction conditions described for the racemic series.

The diastereoisomeric isoxazolines (**11**) and (**12**) were easily separated by flash chromatography and were identified by establishment of the relative configuration of the H5 and H6a-protons. Due to the defined absolute configuration of the C5-carbon from the starting chiral enecarbamate (**10**), we assigned the structure of the diastereoisomer (**11**) using NOESY and NOEDIF techniques (Fig. 2). The diastereoisomer (**12**) does not show correlation between the H5 and H6a-protons in the NOESY spectrum.

The low diastereoselectivity of the 1,3-dipolar cycloaddition is probably due to the dipolar mechanism of the reaction and the distance of the ester group in C5. Similar low selectivity was also verified in some Heck arylation reactions involving chiral enecarbamates,[16] in contrast with [2+2] cycloadditions of these enecarbamates with ketenes.[17]



entry	R	Yield of **11**	Yield of **12**	Ratio of **11** : **12**
1	**a** – Me	37 %	45 %	45:55
2	**b** – Bn	34 %	46 %	43:57

Scheme 3. 1,3-Dipolar cycloaddition of chiral 5-membered endocyclic enecarbamates (**10**). (a) Ethyl chlorooxiimidoacetate, Et_3N, THF, rt.

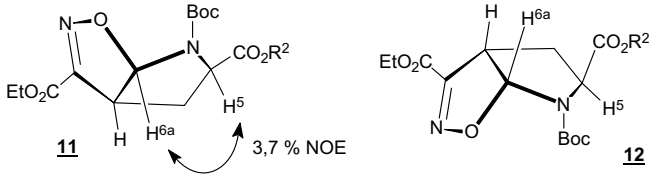
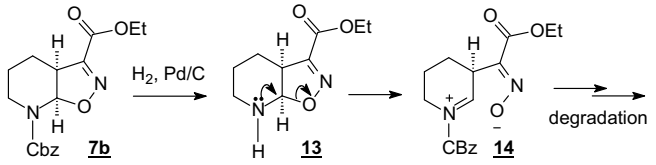
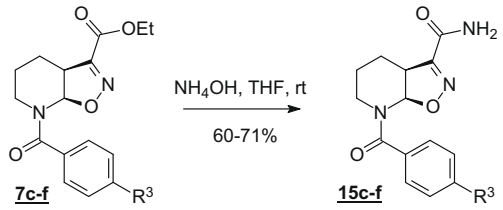


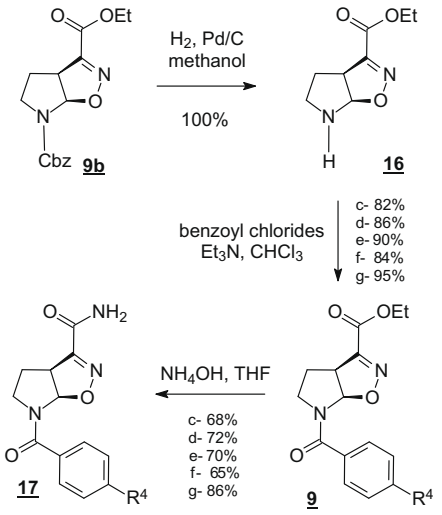
Figure 2. Assignment of the relative configuration of diastereoisomer **11**, by NOEDIF.



Scheme 4. Degradation of unprotected 6-membered isoxazoline amine (**13**).



Scheme 5. Ammonolysis of piperidine isoxazoline cycloadducts (**7c–f**) (R^3: c = NO_2 (60%), d = F (71%), e = OMe (62%), f = ^{t}Bu (68%).



Scheme 6. Synthesis of bisamides (**17**) (R^4: c = NO_2, d = F, e = OMe, f = ^{t}-Bu, g = Cl).

The structures of new 6-membered endocyclic enecarbamates and enamides (**6**), and aza-bicyclic isoxazolines (**7**), (**9**), (**11**), (**12**), (**15**), and (**17**) were fully elucidated by ^{1}H and ^{13}C NMR, FTIR, and HRMS.[18] Although NMR spectra at room temperature are complex, due to the presence of rotamers, some diagnostic signals, that confirm the isoxazoline cycloadduct formation, are present and clear in ^{1}H NMR spectra, such as a doublet or a broad signal near 6.20 ppm for H6a (for **9**, **11**, **12**, and **17**) and H7a (for **7** and **15**) and in ^{13}C NMR spectra, such as a signal near 92 ppm for C6a and C7a, respectively.

The rotamer signals, due to the high rotational barrier of the amide and carbamate bonds, underwent total coalescence, when isoxazoline ^{1}H NMR spectra were obtained at 65 °C.[19] Another peculiarity of the ^{13}C NMR and ^{1}H NMR spectra was the low signal resolution of the bicyclic ring carbons and exocyclic protons of isoxazolines, resulting in broad signals.

Another interesting observation uncovered by this study was the distinctive reactivity of the isoxazoline cycloadducts coming from the 5- and 6-membered enecarbamates during hydrogenolysis.[19] Hydrogenolysis of (**7b**) led to complex mixtures, whereas hydrogenolysis of (**9b**) occurred cleanly to provide the secondary amine (**16**) (Schemes 4 and 6).

We hypothesize that the bicyclic piperidine isoxazoline is more prone to ring opening generating an unstable and very reactive acyliminium intermediate (**14**), which decompose to several unidentified products.

Although cycloadduct (**7b**) could not be used to obtain amides (**15**), they were obtained by direct cycloaddition of the piperideine *N*-(benzoyl)-enamides (**6c–f**), with CEFNO followed by ammonolysis (Scheme 5).[19]

On the other hand, bisamides (**17c–g**) were obtained in a straightforward manner. Carbamate (**9b**) underwent clean hydrogenolysis to provide (**16**), which was acylated with several benzoylchlorides to furnish the corresponding ester-benzamides (**9c–g**).[19] Ammonolysis then converted (**9c–g**) into the corresponding bisamides (**17c–g**) in good overall yields (Scheme 6).

In summary, we explored a new 1,3-dipolar cycloaddition reaction of 5- and 6-membered endocyclic enecarbamates/enamides with nitrile oxides to obtained novel aza-bicyclic 2-isoxazoline compounds, in good yields and in a highly regioselective manner. These new bicyclic systems can be used as potential intermediates in the synthesis of a series of bioactive compounds, such as alkaloids and amino acids. This study also demonstrates the versatility of endocyclic enecarbamates/enamides in organic synthesis and opens up new opportunities for the chemistry of 2-isoxazolines. Studies regarding the anti-inflammatory activity of compounds (**15**) and (**17**), among other isoxazoline derivatives, are in progress and will be reported in due course.

Acknowledgments

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Supplementary data

Representative NMR spectra and experimental procedures for the hydrogenolysis, the ammonolysis, and the N-benzoylation reactions. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.096.

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14. *Typical experimental procedures for 1,3-dipolar cycloaddition:* (a) *For CEFNO 1,3-dipolar cycloadditions*: Ethyl chlorooximidoacetate (CEFNO precursor, 5.1 mmol) is added slowly to a solution of the enecarbamate/enamide (**6**), (**8**), or (**10**) (4.6 mmol) and triethylamine (5.7 mmol) in 15 mL of dry $CHCl_3$ or THF, using a syringe or an addition funnel with a pressure equalizer, over approximately an hour. Next, another equiv of triethylamine and ethyl chlorooximidoacetate is added under the same conditions, if necessary. The

reaction mixture is washed with water (50 mL). THF must be removed before, if used. The aqueous phase is extracted with $CHCl_3$ (2 × 40 mL). The chloroform layers are combined and, after removing the solvent, the residue is submitted to a flash chromatography: silica gel, ethyl acetate/hexane 1:5. Part of the 6-membered enecarbamate/enamide (**6**) is recovered. (b) *For benzonitrile and (2-furfuryl)-formonitrile oxides cycloadditions:* Crude hydroximinoyl chloride (1.64 mmol, in 4 mL of dry $CHCl_3$ is added slowly (40–60 min) to a solution of the enecarbamate/enamide (**6**) or (**8**) (2.46 mmol) and Et_3N (1.97 mmol) in 4 mL of $CHCl_3$. The reaction mixture is maintained under stirring for two additional hours. Excess of enamide/enecarbamate is recovered after usual work up and flash chromatography: silica gel, ethyl acetate/hexane 1:5. The R_f for the cycloadduct on a TLC plate is smaller than that observed for the enamide/enecarbamate (UV, phosphomolybdic acid).

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18. *Representative spectra data for some new compounds:* (**6d**) ^{1}H NMR ($CDCl_3$, δ, 300 MHz, rt): 1.95 and 1.81 (m, 2H, rot), 2.13 (m, 2H); 3.81 and 3.57 (m, 2H, rot), 4.88 and 5.24 (m, 1H, rot), 6.45 and 7.23 (d, J = 8.1 Hz, 1H, rot), 7.10 (m, 2H), 7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, δ, 75 MHz, rt): 21.6 (CH_2), 21.8 (CH_2), 41.2 e 46.7 (CH_2, rot), 108.0 e 110.0 (CH, rot), 115.4 (d, ^2J = 21.6 Hz, CH), 127.3 e 124.7 (CH, rot), 129.9 (C), 130.6 (d, ^3J = 8.4 Hz, CH), 163.7 (d, ^1J = 249 Hz, C–F), 168.2 (C=O). FTIR (neat, cm^{-1}) main bands: 3110, 2920, 2875, 2800, 1633, 1601, 1507, 1409, 1377, 1227, 993, 848, 757, 723, 577. Compound (**7e**) ^{1}H NMR ($CDCl_3$, δ, 300 MHz, rt): 1.36 (t, J = 7.2 Hz, 3H), 1.68–1.93 (m, 4H), 3.21 (m, 1H), 3.36 (m, 1H), 3.82 (s, 3H), 4.29 (br s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 6.33 (br s, 1H), 6.92 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H). ^{13}C NMR ($CDCl_3$, δ, 75 MHz, rt): 14 (CH_3), 18.9 (CH_2), 21.7 (CH_2), 39.5 (CH_2), 41.3 (CH), 55.3 (CH_3), 62.1 (CH_2), 91.6 (CH), 113.8 (CH, aryl), 126.4 (C, aryl), 129.7 (CH, aryl), 155.9 (C, aryl), 160 (C=N), 161.4 (C=O, amide), 172.2 (C=O, ester). FTIR (neat, cm^{-1}) main bands: 3090, 2985, 2958, 1722, 1651, 1606, 1420, 1344, 1251, 1176, 1129, 1024, 921, 843. HRMS-EI (m/z): M^+ calcd for $C_{17}H_{20}N_2O_5$ 332,13722, found 332.12713. Compound (**9d**) ^{1}H NMR ($CDCl_3$, δ, 300 MHz, rt): 1.38 (t, J = 7.0 Hz; 3H), 2.22 (m, 1H), 2.40 (dd, J = 6.0 Hz, J = 13.5 Hz, 1H), 3.20 (br m, 1H), 4.12 (t, J = 8.0 Hz, 1H), 4.35 (br m, 1H), 4.36 (q, J = 7.0 Hz, 2H), 6.22 (br s, 1H), 7.12 (m, 2H), 7.69 (br s, 2H). ^{13}C NMR ($CDCl_3$, δ, 75 MHz, rt): 14.1 (CH_3), 27.9 (CH_2), 43.5 (CH_2), 51.2 (CH), 62.4 (CH_2), 96.2 (CH), 115.6 (d, ^2J = 21.5 Hz, CH), 130.4 (CH), 164.1 (d, ^1J = 250 Hz, C–F), 131 (C), 152.4 (C), 159.8 (C=O), 168.7 (C=O). FTIR (neat, cm^{-1}) main bands: 3030, 2986, 2860, 1721, 1652, 1600, 1509, 1408, 1270, 1131, 931, 853. HRMS-EI (m/z): M^+ calcd for $C_{15}H_{15}FN_2O_4$ 306.10158, found 306.10147. Compound (**9h**) ^{1}H NMR ($CDCl_3$, δ, 300 MHz, rt): 1.33 (s, 9H); 2.00–2.35 (m, 2H); 3.20 and 3.65 (br s, 1H, rot.); 4.23 (m, 1H); 4.46 (m, 1H); 6.25 and 6.98 (br s, 1H, rot.); 7.30–7.50 (m, 4H); 7.52–7.76 (m, 4H). ^{13}C NMR ($CDCl_3$, δ, 75 MHz, rt): 28.2 (CH_2), 31.1 (CH_3), 34.8 (CH), 43.1 (CH_2), 51.6 (C), 94.7 (CH), 125.3 (CH), 126.6 (C), 128.0 (CH), 128.1 (CH), 129.3 (CH), 132.0 (C), 136,4 (C), 154.1 (C), 156.9 (C=N), 169.7 (C=O). FTIR (KBr, cm^{-1}) main bands: 2962, 1635, 1620, 1492, 1411, 1357, 1269, 1176, 1141, 1091, 875, 837. Mp 158–161 °C. HRMS-EI (m/z): M^+ calcd for $C_{22}H_{23}ClN_2O_2$ 382.14480, found 382.14438. Compound (**11b**) ^{1}H NMR ($CDCl_3$, δ, 300 MHz, rt): 1.33 (t, J = 7 Hz, 3H), 1.48 and 1.30 (s, rot., 9H), 2.50 (m, 1H), 2.75 (m, 1H), 4.03 (t, J = 8 Hz, 1H), 4.30 (q, J = 7 Hz, 2H), 4.69 and 4.55 (d, J = 9 Hz, rot., 1H), 5.22–4.90 (m, rot., 2H), 6.48 and 6.35 (d, J = 8 Hz, rot., 1H), 7.33 (br s, 5H). ^{13}C NMR ($CDCl_3$, δ, 75 MHz, rt): 13.9 (CH_3), 27.9 (CH_3), 31.6 and 30.7 (CH_2, rot.), 50.3 and 49.3 (CH, rot.), 58.3 and 57.8 (CH, rot.), 62 (CH_2, ethyl ester), 67.3 (CH_2, benzyl ester), 82 (C, Boc), 94.7 and 94.4 (CH, rot.), 127.8–128.4 (CH, aryl), 135.1 (C, aryl), 151.4 (C=O, Boc), 152.3 (C=N), 159.8 (C=O, ethyl ester), 170.7 and 170.5 (C=O, benzyl ester, rot.). FTIR (neat, cm^{-1}) main bands: 3090, 2980, 2950, 1720 (bb), 1570, 1455, 1392, 1260, 1165, 1140, 1032, 900. HRMS-EI (m/z): M^+ calcd for $C_{21}H_{26}N_2O_7$ 418.17400, found 418.17390. Compound (**12b**) ^{1}H NMR ($CDCl_3$, δ, 300 MHz, rt): 1.36 (t, J = 7.2 Hz, 3H), 1.49 and 1.35 (s, rot. 9H), 2.35 (m, 1H), 2.54 (m, 1H), 4.01 (m, 1H), 4.36 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 5.16 (m, rot. 2H), 6.53 and 6.37 (d, J = 7.8 Hz, rot.), 7.34 (br s, 5H). ^{13}C NMR ($CDCl_3$, δ, 75 MHz, rt): 13.9 (CH_3), 27.8 and 28.0 (CH_3, rot.), 32.2 and 33.3 (CH_2, rot.), 48.2 and 49.3 (CH, rot.), 58.5 and 59.1 (CH, rot.), 62.2 (CH_2, ethyl ester), 67.2 (CH_2, benzyl ester), 82.1 (C, Boc), 95.6 and 96.5 (CH, rot.), 128.2-128.6 (CH, aryl), 134.8 and 135.1 (C, aryl), 152.2 and 152.5 (C=O, Boc, rot.), 152.7 (C=N), 159.7 (C=O, ethyl ester), 170.8 and 171.3 (C=O, benzyl ester, rot.). FTIR (neat, cm^{-1}) main bands: 3080, 2980, 2940, 1750, 1725, 1595, 1452, 1380, 1252, 1180, 1039. HRMS-EI (m/z): M^+ calcd for $C_{21}H_{26}N_2O_7$ 418.17400, found 418.17385. Compound (**17g**) ^{1}H NMR (DMSO-d_6, δ, 300 MHz, rt): 2.18 (br m, 2H), 3.15 and 3.48 (br m, 1H, rot.), 4,19 (br m, 2H), 6.17 and 6.66 (d, J = 7.2 Hz, 1H, rot.), 7.58 (br s, 4H); 7.69 (s, 1H), 7.94 (s, 1H). ^{13}C NMR (DMSO-d_6, δ, 75 MHz, rt): 26.8 (CH_2), 43.5 (CH_2), 51.9 (CH), 94.5 (CH), 128.5 (CH, aryl), 129.6 (C, aryl), 134.2 (CH, aryl), 135.3 (C, aryl), 152.2 (C=N), 160.5 (C=O, amide), 167.9 (C=O, amide). FTIR (KBr, cm^{-1}) main bands: 3310, 3172, 2990, 2870 1665, 1641, 1410, 841. Mp: 221–223 °C. HRMS-EI (m/z): M^+ calcd for $C_{13}H_{12}ClN_3O_3$ 293.05671, found 293.05628.
19. See the experimental procedures or spectra in the online version.