An Alternative Route to Pyrrolotriazoles and other *N*-Bridgehead Heterocycles

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Received 26 February 2006

Abstract: 1,2-Diaza-1,3-butadienes bearing a Boc moiety at N-1 react with acetonitrile derivatives to afford 1-Boc-protected 1,2-diaminopyrroles that represent, by flexible condensation–deprotection or deprotection–condensation steps, a flexible entry to different N-bridgehead heterocycles.

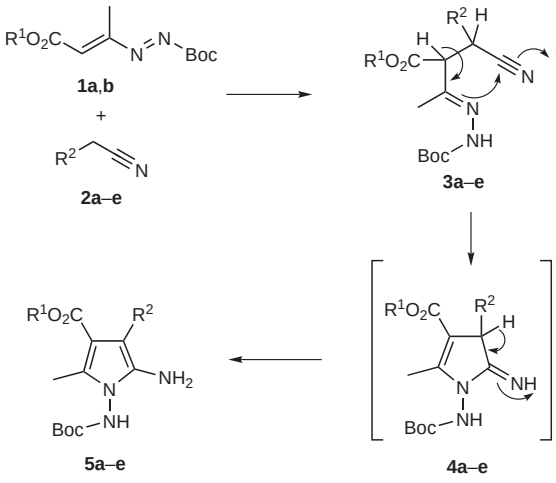
Key words: 1,2-diaza-1,3-butadienes, protecting groups, nitriles, pyrroles, fused-ring systems

1,2-Diaza-1,3-butadienes[1a–d] represent an important class of powerful intermediates in organic synthesis as Michael acceptor reagents owing to the presence of the conjugated heterodiene system.[1e–i] Among them of particular interest are *tert*-butyl (3-alkoxy-1-methyl-3-oxoprop-1-enyl)diazenecarboxylate derivatives **1a**,**b** (Scheme 1) that directly introduce the Boc group into a variety of heterocycles bearing an amino function and/or nitrogen heteroatom.[2] The Boc group is still one of the most widely used in synthetic organic chemistry when it is required to protect amino function due to its easy removal.[3]

The nucleophilic attack of the activated methylene group of acetonitrile derivatives **2a**–**e** at the aza–ene system of **1a**,**b** affords hydrazone 1,4-adducts **3a**–**e**. By means of intramolecular ring closure on the nitrile function we achieved 1-Boc-protected 1,2-diaminopyrrole derivatives **5a**–**e** (Scheme 1).[4,5]

We considered of interest their use as building blocks in a synthetic pathway to afford different N-bridgehead heterocycles useful as intermediates in drug discovery, agrochemicals, photographic materials and dyes.[6] A literature survey shows that the synthesis of pyrrolo[1,2-*b*][1,2,4]triazole derivatives involves cyclocondensation reaction of appropriately functionalised triazole derivatives to form the fused pyrrole ring.[7] Herein we propose an alternative route to this heterocyclic pattern via 1-Boc-protected 1,2-diaminopyrroles.

Pyrrole derivatives **5a**,**b** reacted with orthoesters **6a**,**b** under solvent-free conditions to produce pyrrolo[1,2-*b*][1,2,4]triazole derivatives **8a**–**d**[8] through iminoether intermediates **7a**–**d**[8] (Scheme 2, Table 1). The reaction can be performed more conveniently in a one-pot procedure without the isolation of **7**.



5a R^1 = Et; R^2 = CN
5b R^1 = Et; R^2 = PiperidineCO
5c R^1 = Et; R^2 = 4-$NO_2C_6H_4$
5d R^1 = Et; R^2 = 2,4-$Cl_2C_6H_3$
5e R^1 = Me; R^2 = 4-ClC_6H_4NHCO

Scheme 1

The same conditions applied to **5e**[5b] afforded a new approach to pyrrolo[2,3-*d*]pyrimidin-4-one derivatives[9] **9a**,**b**[10] by means of intramolecular ring closure owing to the amidic NH on the iminoether function of **7e**,**f**[10] and successive Boc removal. In this case the preliminary deprotection of the 1-amino function to produce 1,2-diaminopyrrole derivative **10**[10] and subsequent condensation with orthoesters **6a**,**b** represents a convenient means of obtaining pyrrolo[1,2-*b*][1,2,4]triazole derivatives **8e**,**f**[10] (Scheme 2, Table 1).

In order to widen the scope of this approach towards different N-bridgehead heterocycles, we explored the one-pot reaction between pyrrole derivatives **5a**–**d**[5b] and methyl pyruvate under acidic heterogeneous catalysis with Amberlyst 15H to achieve pyrrolo[1,2-*b*][1,2,4]triazin-3-one[11] derivatives **11a**–**d**[12] in 65–82% yields (Scheme 3).

With the aim of affording derivatives bearing the pyrrolotriazine skeleton with a different position of the carbonyl group in respect to **11a**,**b** or various degrees of saturation, we planned the selective alkylation at the 1-amino function of **5a** with ethyl 2-bromoacetate (**12a**) or phenacyl bromide (**12b**) to obtain **13a**,**b**[13] in good yields (80–83%, Scheme 4). We found that for **13a** both thermal Boc

SYNLETT 2006, No. 11, pp 1734–1738
Advanced online publication: 04.07.2006
DOI: 10.1055/s-2006-947324; Art ID: D06306ST
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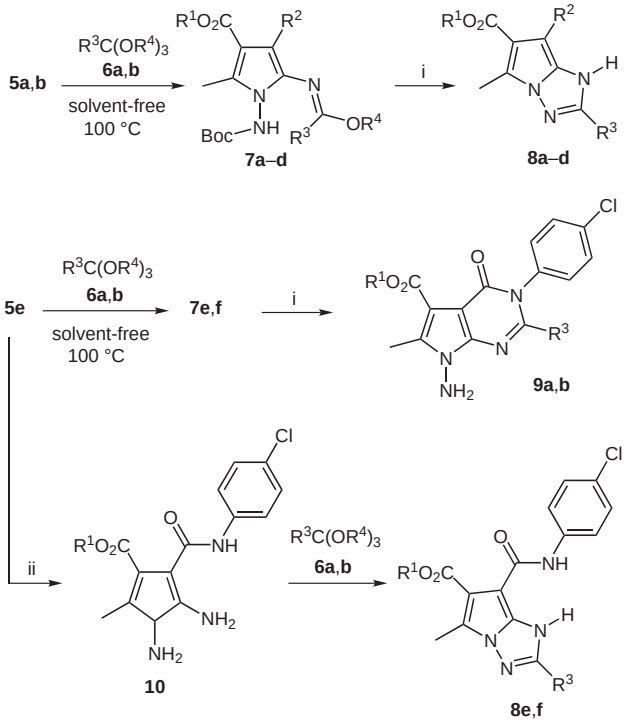
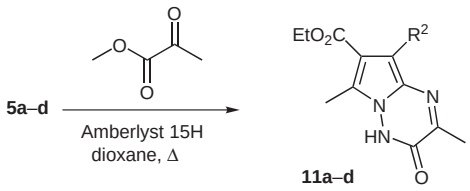
Table 1 Synthesis of Pyrrolo[1,2-*b*][1,2,4]triazoles **8a–f** and Pyrrolo[2,3-*d*]pyrimidin-4-ones **9a**,**b**

Pyrrole **5**			Orthoester **6**			Product **7**		Product **8**		Product **9**	
	R^1	R^2		R^3	R^4		Yield (%)[a]		Yield (%)[a]		Yield (%)[a]
5a	Et	CN	**6a**	H	Et	**7a** (**5a** + **6a**)	80	**8a**	58	**9a** (**5e** + **6a**)	90
5b	Et	PiperidineCO	**6b**	Me	Me	**7b** (**5a** + **6b**)	85	**8b**	61	**9b** (**5e** + **6b**)	94
5e	Me	4-ClC_6H_4NHCO				**7c** (**5b** + **6a**)	68	**8c**	55		
						7d (**5b** + **6b**)	79	**8d**	58		
						7e (**5e** + **6a**)	78	**8e** (**10** + **6a**)	60		
						7f (**5e** + **6b**)	68	**8f** (**10** + **6b**)	86		

[a] Yield of pure isolated products.



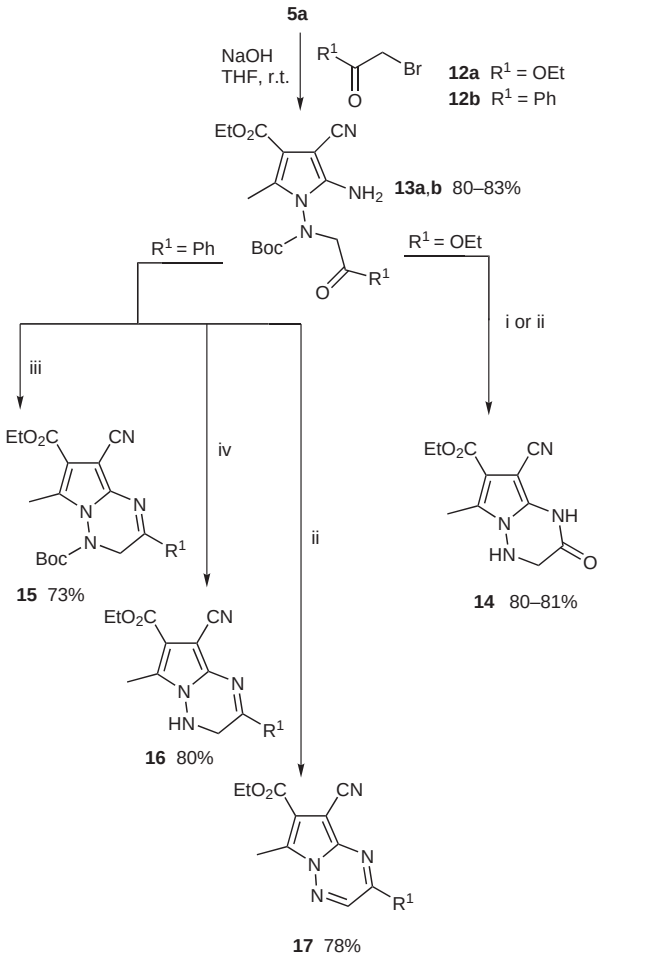
Scheme 2 *Reagents and conditions*: i) 180 °C; ii) Amberlyst 15H, refluxing dioxane, 4 h.



11a R^2 = CN, 79%
11b R^2 = PiperidineCO, 68%
11c R^2 = 4-$NO_2C_6H_4$, 65%
11d R^2 = 2,4-$Cl_2C_6H_3$, 82%

Scheme 3

removal and treatment with Amberlyst 15H in refluxing dioxane led to pyrrole[1,2-*b*][1,2,4]triazin-2-one derivative **14**[12] in comparable yields (80–81%). By varying the reaction conditions, **13b** can give rise to different pyrrole[1,2-*b*][1,2,4]triazine derivatives **15**,[13] **16**,[13] and **17**[13] in good yields (Scheme 4). In particular, derivative **17** is thus obtained as the sole regioisomer by a different reaction pathway and in a more satisfactory yield than previously reported.[5a]



Scheme 4 *Reagents and conditions*: i) 180 °C; ii) Amberlyst 15H, refluxing dioxane; iii) Amberlyst 15H, refluxing THF; iv) TFA, CH_2Cl_2, 0 °C.

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In summary, we report herein an improved and flexible condensation–deprotection or deprotection–condensation sequence of 1-Boc-protected 1,2-diamminopyrroles with orthoesters and different carbonyl compounds for the synthesis of target N-bridgehead heterocycles such as pyrrolotriazole and pyrrolotriazine derivatives that represent the core of compounds of potential usefulness in medicinal[14] and technological fields.[15]

Acknowledgment

This work was supported by financial assistance from the M.I.U.R.-Roma (PRIN 2004), and the Università degli Studi di Urbino 'Carlo Bo'.

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(8) **Procedure for the Preparation of Derivatives 7b and 8b.** Pyrrole derivative **5a** (308 mg, 1 mmol) and **6b** (4 mL) were heated at 100 °C in an oil bath under magnetic stirring for 5 h. Then, **6b** was removed under reduced pressure and the residue was heated at 180 °C in an oil bath for 30 min. The resulting dark residue was treated with THF and Et_2O to afford **8b** as a light grey powder that was recrystallised as a white powder from hot EtOH. Analytical data of **8b**: mp 221–222 °C. IR (nujol): 3203, 3176, 2220, 1673, 1620, 1562 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.29 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3), 2.42 (s, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 4.23 (q, *J* = 6.8 Hz, 2 H, OCH_2CH_3), 13.43 (br s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.31, 11.99, 14.21, 59.78, 59.89, 111.88, 115.71, 120.37, 137.98, 153.76, 163.11. MS: *m/z* (%) = 232 (28) [M^+], 203 (100), 187 (20), 159 (9). Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.72; H, 5.26; N, 24.43.
Derivative **7b** was isolated in a separate experiment by stopping the reaction after heating at 100 °C for 5 h and removing **6b** under reduced pressure. The oily residue was treated with Et_2O–light PE to obtain **7b** as a beige powder. Analytical data of **7b**: mp 160 °C (dec.). IR (nujol): 3260, 2220, 1734, 1677, 1658, 1552 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.41 (s, 9 H, *t*-BuO), 1.99 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 10.32 (br s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.12, 13.99, 17.17, 27.60, 54.25, 59.84, 77.64, 81.28, 106.86, 115.23, 134.89, 146.04, 154.31, 162.36, 168.42. MS: *m/z* (%) = 364 (38) [M^+], 308 (100), 264 (88), 235 (63), 192 (58). Anal. Calcd for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 55.87; H, 6.68; N, 15.18.

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(10) Analytical data of **7f**: white powder from Et_2O–cyclohexane, mp 167 °C (dec.). IR (nujol): 3211, 3178, 1746, 1664, 1645, 1616, 1556 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.40 (s, 9 H, *t*-BuO), 1.84 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 3.66 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 7.30 (d, *J* = 8.8 Hz, 2 H, Ar), 7.63 (d, *J* = 8.8 Hz, 2 H, Ar), 10.10 (s, 1 H, NH), 10.35 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.57, 17.27, 27.71, 51.16, 53.59, 80.74, 102.78, 105.67, 120.60, 126.11, 128.39, 133.43, 138.73, 139.92, 154.50, 162.40, 165.36, 167.74. MS: *m/z* (%) = 478 (13) [M^+], 296 (100), 252 (21), 220 (19). Anal. Calcd for $C_{22}H_{27}N_4O_6Cl$: C, 55.17; H, 5.68; N, 11.70. Found: C, 55.03; H, 5.72; N, 11.65. Analytical data of **8f**: white powder from EtOAc–cyclohexane, mp 235–239 °C (dec.). IR (nujol): 3393, 3075,

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1670, 1635, 1588, 1555 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.41 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 7.36 (d, *J* = 8.0 Hz, 2 H, Ar), 7.68 (d, *J* = 8.0 Hz, 2 H, Ar) 11.81 (s, 1 H, NH), 12.95 (br s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.48, 11.83, 52.07, 89.38, 107.69, 120.12, 121.85, 125.93, 128.76, 138.61, 154.38, 160.89, 168.71. MS: *m/z* (%) = 346 (25) [M^+], 220 (71), 188 (74), 169 (100). Anal. Calcd for $C_{16}H_{15}N_4O_3Cl$: C, 55.42; H, 4.36; N, 16.16. Found: C, 55.46; H, 4.14; N, 16.01.

Analytical data of **9b**: beige powder from hot EtOAc, mp 228–229 °C (dec.). IR (nujol): 3326, 3270, 3217, 3054, 1692, 1681, 1615, 1563, 1532 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.11 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3), 3.66 (s, 3 H, OCH_3), 5.87 (s, 2 H, NH_2), 7.39 (d, *J* = 8.4 Hz, 2 H, Ar), 7.61 (d, *J* = 8.4 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.60, 23.90, 50.76, 100.23, 102.91, 129.45, 130.64, 133.28, 137.48, 139.98, 145.97, 153.79, 156.49, 164.40. MS: *m/z* (%) = 346 (20) [M^+], 314 (58), 299 (40), 271 (13), 152 (100), 111 (70). Anal. Calcd for $C_{16}H_{15}N_4O_3Cl$: C, 55.42; H, 4.36; N, 16.16. Found: C, 55.27; H, 4.12; N, 16.22.

Analytical data of **10**: beige powder from dioxane, mp 221–222 °C (dec.). IR (nujol): 3464, 3344, 3195, 1661, 1641, 1594, 1546 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 5.53 (s, 2 H, NH_2), 6.48 (s, 2 H, NH_2), 7.33 (d, *J* = 8.5 Hz, 2 H, Ar), 7.63 (d, *J* = 8.5 Hz, 2 H, Ar), 11.93 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 12.11, 51.83, 89.12, 101.66, 119.91, 125.24, 128.49, 135.22, 138.69, 148.59, 163.49, 168.18. MS: *m/z* (%) = 322 (4) [M^+], 290 (13), 196 (12), 168 (28), 153 (56), 127 (100). Anal. Calcd for $C_{14}H_{15}N_4O_3Cl$: C, 52.10; H, 4.68; N, 17.36. Found: C, 52.26; H, 4.82; N, 17.09.

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(12) **Representative Procedure for the Preparation of Derivative 11d.**

Pyrrole derivative **5d** (428 mg, 1 mmol) and methyl pyruvate (135 mg, 1.323 mmol) were refluxed in dioxane (4 mL) in the presence of Amberlyst 15H (400 mg) for 2 h. Then the resin was removed by filtration and the solvent evaporated under reduced pressure. The residue, treated with Et_2O, gave derivative **11d** as a yellow powder.

Analytical data of **11d**: mp 226–229 °C. IR (nujol): 3129, 3077, 1706, 1679, 1578 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 0.96 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 2.27 (s, 3 H, CH_3), 2.60 (s, 3 H, CH_3), 3.97 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 7.29 (d, *J* = 8.4 Hz, 1 H, Ar), 7.38 (d, *J* = 8.4 Hz, 1 H, Ar), 7.60 (s, 1 H, Ar), 12.19 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.64, 13.61, 17.39, 59.19, 95.53, 110.21, 123.49, 126.36, 126.53, 128.06, 130.84, 132.16, 134.38, 135.70, 150.23, 151.82, 164.02. MS: *m/z* (%) = 379 (75) [M^+], 350 (100), 344 (58), 316 (91). Anal. Calcd for $C_{17}H_{15}N_3O_3Cl_2$: C, 53.70; H, 3.98; N, 11.05. Found: C, 53.58; H, 3.72; N, 11.18.

(13) **Preparation of Derivative 13a.**

Pyrrole derivative **5a** (308 mg, 1 mmol) and NaOH (100 mg, 2.5 mmol) were suspended in THF (4 mL) and magnetically stirred for 10 min at r.t. Then **12a** (334 mg, 2 mmol) was added to the reaction mixture and the stirring was continued for 30 min; THF was removed under reduced pressure and the residue was dissolved in EtOAc and washed with H_2O in a separatory funnel. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure; the solid residue was recrystallised from hot EtOAc to give **13a** as a white powder.

Analytical data of **13a**: mp 155–157 °C (dec.). IR (nujol): 3347, 3321, 3244, 3205, 2214, 1742, 1724, 1699, 1652, 1590 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.15–1.26 (m, 6 H, 2 OCH_2CH_3), 1.29 and 1.38 (2 s, 9 H, *t*-BuO), 2.24 and 2.27 (2 s, 3 H, CH_3), 4.11–4.20 (m, 4 H, OCH_2CH_3), 4.40–4.60 (m, 2 H, CH_2), 6.49 (s, 2 H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.95, 14.09, 27.44, 51.51, 52.77, 59.54, 61.46, 65.52, 82.57, 83.07, 105.92, 116.40, 131.40, 148.09, 151.69, 152.06, 162.76, 169.62, 169.86. MS: *m/z* (%) = 394 (15)[M^+], 338 (100), 293 (18), 265 (26), 192 (88). Anal. Calcd for $C_{18}H_{26}N_4O_6$: C, 54.81; H, 6.64; N, 14.20. Found: C, 54.67; H, 6.38; N, 14.34.

Analytical data of **14**: white powder from hot EtOH, mp 246–250 °C (dec.). IR (nujol): 3250, 3114, 2218, 1699, 1612, 1567 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.26 (t, *J* = 6.5 Hz, 3 H, OCH_2CH_3), 2.35 (s, 3 H, CH_3), 3.70 (d, *J* = 8.0 Hz, 2 H, CH_2), 4.20 (q, *J* = 6.5 Hz, 2 H, OCH_2CH_3), 6.79 (t, *J* = 8.0 Hz, 1 H, NH), 11.68 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.93, 14.06, 49.28, 59.66, 71.57, 106.63, 114.08, 132.04, 136.00, 162.57, 165.62. MS: *m/z* (%) = 248 (87) [M^+], 219 (61), 203 (27), 164 (100). Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.34; H, 4.96; N, 22.37.

Preparation of Derivative 13b.

Pyrrole derivative **5a** (308 mg, 1 mmol) and NaOH (50 mg, 1.25 mmol) were suspended in THF (4 mL) and magnetically stirred for 10 min at r.t. Then, **12b** (229 mg, 1.15 mmol) was added to the reaction mixture and the stirring was maintained for 24 h. The reaction work-up was the same as for **13a**. The crude was recrystallised from EtOAc–light PE to obtain **13b** as a white powder.

Analytical data of **13b**: mp 157 °C (dec.). IR (nujol): 3327, 3243, 3194, 2220, 1726, 1703, 1693, 1650, 1592 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.26 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3), 1.30 and 1.33 (2 s, 9 H, *t*-BuO), 2.32 and 2.35 (2 s, 3 H, CH_3), 4.19 (q, *J* = 6.8 Hz, 2 H, OCH_2CH_3), 5.13 and 5.15 (2 overlapped d, *J* = 18.4 Hz, 1 H, $COCH_aCH_b$), 5.51 (d, *J* = 18.4 Hz, 1 H, $COCH_aCH_b$), 6.60 and 6.63 (2 s, 2 H, NH_2), 7.60 (t, *J* = 7.6 Hz, 2 H, Ar), 7.72 (t, *J* = 7.6 Hz, 1 H, Ar), 8.04 (d, *J* = 7.6 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.70, 14.70, 14.81, 28.13, 28.29, 57.25, 58.29, 60.25, 66.14, 83.09, 83.51, 106.58, 117.15, 128.92, 129.65, 132.09, 134.99, 149.08, 152.64, 152.92, 163.49, 196.03, 196.62. MS: *m/z* (%) = 426 (7) [M^+], 370 (60), 352 (62), 192 (50), 164 (100). Anal. Calcd for $C_{22}H_{26}N_4O_5$: C, 61.96; H 6.15; N, 13.14. Found: C, 61.72; H, 6.24; N, 13.26.

Preparation of Derivative 15.

Compound **13b** (426 mg, 1 mmol) was refluxed in THF (5 mL) in the presence of Amberlyst 15H (400 mg) for 12 h. The resin was removed by filtration, THF was evaporated under reduced pressure and treated with Et_2O to obtain a yellow residue. The crude was recrystallised from MeOH to furnish **15** as light orange crystals.

Analytical data of **15**: mp 137–139 °C (dec.). IR (nujol): 3070, 2227, 1751, 1707, 1539 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.20–1.33 (m, 12 H, OCH_2CH_3 and *t*-BuO), 2.45 (2 s, 3 H, CH_3), 4.28 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.40 (d, *J* = 17.2 Hz, 1 H, CH_aCH_b), 5.62 (d, *J* = 17.2 Hz, 1 H, CH_aCH_b), 6.60 and 6.63 (2 s, 2 H, NH_2), 7.56–7.65 (m, 3 H, Ar), 8.09 (d, *J* = 8.4 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.20, 14.71, 27.91, 47.32, 60.93, 85.91, 85.98, 109.81, 114.53, 127.98, 129.84, 133.42, 134.86, 135.89, 138.57, 154.98, 162.85, 164.22. MS: *m/z* (%) = 408 (11) [M^+], 352 (100), 323 (19), 307 (13). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.71; H, 5.92; N, 13.69.

Preparation of Derivative 16.

Compound **13b** (426 mg, 1 mmol) was dissolved at 0 °C in a mixture of CH_2Cl_2–TFA (1:1, 8 mL) and maintained at the same temperature for 2.75 h. Then the solvent was removed under reduced pressure and the residue was treated with

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Et_2O to obtain a yellow powder that was recrystallised from $CHCl_3$–light PE to give pure derivative **16**.
Analytical data of **16**: mp 202–203 °C (dec.). IR (nujol): 3258, 2215, 1682, 1550 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3), 2.45 (s, 3 H, CH_3), 4.25 (q, *J* = 6.8 Hz, 2 H, OCH_2CH_3), 4.31 (d, *J* = 8.8 Hz, 2 H, CH_2), 6.37 (t, *J* = 8.8 Hz, 1 H, NH), 7.50–7.60 (m, 3 H, Ar), 8.07 (d, *J* = 8.4 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.91, 14.12, 43.91, 59.89, 84.49, 108.47, 114.60, 127.18, 128.90, 131.99, 133.81, 134.86, 139.16, 162.85. MS: *m/z* (%) = 308 (82) [M^+], 277 (100), 250 (42). Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.18; H, 5.26; N, 18.19.

Preparation of Derivative 17.
Compound **13b** (426 mg, 1 mmol) was refluxed in dioxane (5 mL) in the presence of Amberlyst 15H (400 mg) for 8 h. The resin was removed by filtration and dioxane was evaporated under reduced pressure. The residue, treated with Et_2O, furnished pure derivative **17** as red-orange crystals in a 78% yield, with analytical data as previously reported.

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