Facile Direct Synthesis of Acetylenedicarboxamides

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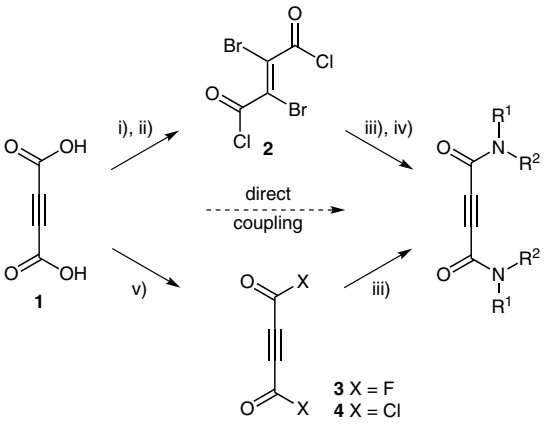
Abstract: A convenient, rapid and widely applicable one-pot procedure has been developed for the synthesis of acetylenedicarboxamides from various primary and secondary amines, including amino acid derivatives, protected carbohydrates, and fluorescent labels. By using DMTMM for amide coupling, acetylenedicarboxylic acid was directly converted into acetylenedicarboxamides in highly competitive overall yields (52–80%).

Key words: alkynes, amides, carboxylic acids, coupling, condensation

Acetylenedicarboxylic acid (ADA, **1**) and its derivatives are widely used compounds in the synthesis of carbo- and heterocycles. In the case of acetylenedicarboxylic acid diesters the electron-deficient triple bond readily reacts as a dipolarophile or dienophile in thermal cycloadditions, and as a conjugate acceptor in Michael additions.[1] Often, both types of reaction pathways are involved in the synthesis of heterocyclic systems when using ADA derivatives.[2] As part of our ongoing research on the multidecoration of nanoscaffolds by 'click'-type conjugation reactions,[3] in particular by using ADA diesters as both functionalizing and branching elements,[3a] we were interested in acetylenedicarboxylic diamides (ADCAs) as chemically more stable analogues of diesters. However, the formation of amides of ADA **1** suffers from competing and/or subsequent Michael additions of the amine component because of the highly electrophilic nature of the conjugated triple bond. Only a few general protocols for the preparation of ADCAs have been described (Scheme 1) that are based on acid halides such as dibromofumaroyl dichloride (**2**)[4] or acetylenedicarbonyl difluoride (**3**).[5] Reports on the use of acetylenedicarbonyl dichloride (**4**) remain controversial,[6] with only few applications for the synthesis of ADCAs;[7] mixed anhydrides of **1** tend to polymerize.[8] All these protocols require several steps and involve sensitive reagents or intermediates. The widely applied standard technique for direct amide coupling using carbodiimides seems to be generally inefficient in the case of **1**,[9] and our attempts to prepare ADCAs via carbonyldiimidazole activation[10] also resulted in no product formation.

On the assumption that ADA deprotonation should render the triple bond more electron rich[11] and hence more stable to conjugate nucleophilic attack by amines, we, therefore, searched for a coupling reagent that involves the incipient formation of an ionic ammoniumcarboxylate intermediate in the reaction mechanism.



Scheme 1 Common strategies for the synthesis of acetylenedicarboxamides: *Reagents and conditions*: (i) Br_2; (ii) PCl_5; (iii) R^1NHR^2; (iv) Zn; (v) SF_4 (X = F) or $SOCl_2$ (X = Cl).

From the broad range of peptide-coupling reagents[12] 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM, **5**),[13] which is commercially available or can be readily prepared from cyanuric chloride in two steps,[14,15] seemed to be a reagent that could fulfill this condition. Indeed, when using a slightly modified Kunishima protocol[15] for a test reaction of **1** with 2-phenylethylamine (**6a**) in tetrahydrofuran the desired N^1,N^4-diphenethylbut-2-ynediamide (**7a**) was isolated in 59% yield.

However, the addition of amines to **1** dissolved in tetrahydrofuran or ethyl acetate[16] often resulted in the formation of gummy gels, and the yields proved to be erratic. In the search for a better solvent, the latter needed to dissolve polar and/or ionic starting materials, intermediates, and products, but not decompose DMTMM **5**. From test reactions [0.05 M **1**, **6a** (1.1 equiv), **5** (1.5 equiv), 20 °C, 5 h, workup A] with methanol,[17] *N*,*N*-dimethylformamide,[18] or *N*-methylpyrrolidin-2-one[19] as the solvents, the use of methanol gave only low yields of **7a** (16%) whereas *N*,*N*-dimethylformamide or *N*-methylpyrrolidin-2-one gave promising results (DMF, 48%; NMP, 52%). Aqueous (10%, v/v) solvent mixtures gave significantly lower yields than neat organic solvents, and no diamide product was isolated from reactions in pure water. *N*-Methylpyrrolidin-2-one was finally chosen as the solvent for all further investigations because isolated yields on average were slightly higher. Concentrations of **1** in *N*-methylpyr-

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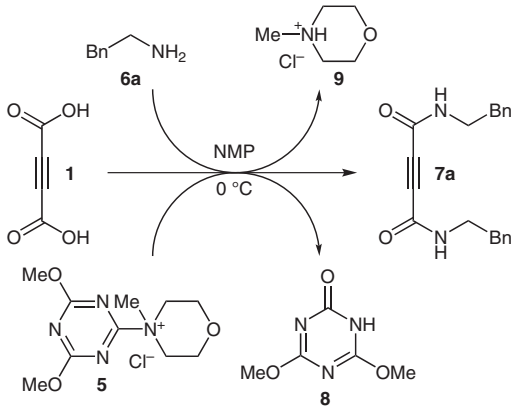
rolidin-2-one as high as 0.3 M were used to reduce the total volume, and reactions were conducted at 0 °C to avoid decomposition of dissolved **1** and to minimize the decomposition of reagent **5**.[15] Under the improved conditions [0.3 M **1**, amine (1.1 equiv), **5** (1.5 equiv), 0 °C, 5 h] pure diamide **7a** was isolated in 73% yield (Scheme 2).



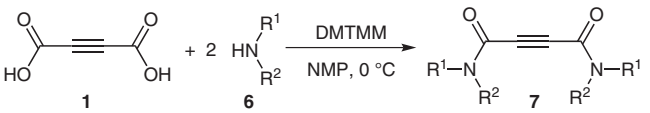
Scheme 2 Synthesis of diamide **7a** by direct coupling of acetylenedicarboxylic acid (**1**) and 2-phenylethylamine (**6a**) promoted by the DMTMM reagent **5**

Indeed, a variety of primary and secondary amines or their respective ammonium salts were also directly converted into the corresponding dicarboxamides (Table 1). Only sterically hindered amines [e.g., dicyclohexylamine (**6p**)] or amines with low nucleophilicity [e.g., 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**6z**)] gave low yields of the corresponding ADCAs under such conditions.

The crude product often contained significant amounts of the byproduct 6-dimethoxy-1,3,5-triazin-2(1*H*)-one (**8**) despite extensive aqueous extraction, which can render purification challenging. In most cases it was found helpful to first remove most of **8** by crystallization from tetrahydrofuran, followed by product purification from the remaining crude mixture by chromatography and/or recrystallization. While screening reactions were usually performed on a 5-mmol scale, an exemplary 40-mmol preparative scale-up with amine **6a** proceeded without a decrease in the yield. Considering that the synthesis requires two successive coupling steps, overall yields of ADCAs **7a**–**y** are quite satisfactory.

The ADCAs are mostly solids (except for **7m** and **7n**) and crystallize as fine needles. Because of the partial double-bond character of the amide bond that causes diastereomer formation, nitrogen substituents can give up to four sets of signals in their ^{1}H and ^{13}C NMR spectra. Monoalkylamides (e.g., **6a**) show one strong signal set corresponding to the predominating *cis*/*cis* conformer[20] and only minor other sets, while diamides of symmetrical dialkylamines (e.g., **7m**) display only two signal sets. Spectra of ADCAs from unsymmetrical dialkylamines (e.g., **7r**) show four sets of ^{1}H NMR signals with almost identical relative intensities.

Table 1 One-Pot Synthesis of Diamides **7** from Acetylenedicarboxylic Acid (**1**) and Various Amines Using DMTMM **5**



Entry	Amine R^1R^2NH	Product	Yield (%)
1	**6a** $Ph(CH_2)_2NH_2$	**7a**	73
2	**6b** $PrNH_2$	**7b**[5]	59
3	**6c** $BuNH_2$	**7c**	63
4	**6d** $Me(CH_2)_5NH_2$	**7d**	67
5	**6e** $allylNH_2$	**7e**[5]	62
6	**6f** $propargylNH_2$	**7f**	80
7	**6g** $BnNH_2$	**7g**[5]	72
8	**6h** piperonylamine	**7h**	62
9	**6i** $CyNH_2$	**7i**[5]	68
10	**6j** (*R*)-1-phenylethylamine	**7j**	70
11	**6k** $PhNH_2$	**7k**	54
12	**6l** $4\text{-}MeOC_6H_4NH_2$	**7l**	61
13	**6m** Bu_2NH	**7m**[4,5]	67
14	**6n** $(allyl)_2NH_2$	**7n**	52
15	**6o** Bn_2NH	**7o**	69
16	**6p** Cy_2NH	**7p**	trace
17	**6q** pyrrolidine	**7q**[4,5]	58
18	**6r** BnNHMe	**7r**	63
19	**6s** H-Gly-OEt·HCl	**7s**	64
20	**6t** H-Leu-OMe·HCl	**7t**	71
21	**6u** H-Phe-OMe·HCl	**7u**	65
22	**6v** H-D-Phg-OMe·HCl	**7v**	69
23	**6w** L-(–)-ephedrine	**7w**	65
24	**6x** $dansylNH(CH_2)_3NH_2$	**7x**	61
25	**6y** Ac_5-β-D-Gal*p*-$O(CH_2)_2NH_2$·TosOH	**7y**	59
26	**6z** Ac_5-β-D-Glc*p*-NH_2	**7z**	trace

In conclusion, a mild and rather general one-pot procedure has been developed that allows the direct conversion of **1** with free amines or their ammonium salts into the corresponding ADCA in good overall yields by using DMTMM **5** in *N*-methylpyrrolidin-2-one as the coupling reagent, with minimal loss of material from competing Michael reactivity.

Starting materials and reagents were purchased from commercial suppliers and used without purification. Analytical TLC was performed on silica gel F_{254} (E. Merck, Darmstadt) with UV detection followed by charring with $KMnO_4$ or anisaldehyde stain. Column chromatography was performed using silica gel 60 (0.06–0.2 mm; Roth, Karlsruhe). Petroleum ether = PE. NMR spectra were recorded on Bruker DRX 500 or Bruker 300 MHz Avance II spectrometers at r.t. FT-IR spectra were measured by Perkin-Elmer Paragon 1000 PC. ESI-MS spectra were recorded using a Bruker-Franzen Esquire-LC mass spectrometer and EI-MS spectra with Varian MAT 212. Combustion analysis was performed on an Elementar Vario EL instrument. Melting points were measured on a Büchi SMP-20 apparatus and are uncorrected.

Reaction of 1 with Amines; General Procedure

To a stirred solution of acetylenedicarboxylic acid (**1**, 0.57 g, 5 mmol) in NMP (10 mL) at 0 °C a solution of the amine (12 mmol, 2.4 equiv) in NMP (5 mL) [for ammonium salts additionally NMM (2 mL) was used] was added dropwise. After 10 min DMTMM **5** (4.0 g, 14 mmol, 2.8 equiv) was added and the mixture was stirred for 5 h.

Workup A: The mixture was partitioned between EtOAc and H_2O (100 mL each), and the organic layer was washed successively with brine (100 mL), sat. $NaHCO_3$ (100 mL), 1 M HCl (100 mL), and brine (2 × 100 mL) [for compounds **7b**,**q**,**s**–**v**,**y** brine was used instead of H_2O, and the organic phase was washed with brine (4 × 100 mL) only]. The solution was dried ($MgSO_4$), the solvent was evaporated, and the residue was dissolved in a small amount of refluxing THF. The major portion of 6-dimethoxy-1,3,5-triazin-2(1*H*)-one (**8**) was crystallized at –20 °C, and the liquid phase containing the product was separated and evaporated. The remaining residue was further purified by column chromatography and/or recrystallization as appropriate.

Workup B: The mixture was poured into 1 M HCl (150 mL; for compounds **7h**,**x** H_2O was used instead) with stirring at 0 °C, and stirring was continued for 15 min. The resulting solid was collected by filtration, washed with H_2O, and dried under vacuum. The residue was dissolved in a small amount of refluxing THF and further purified as described above, except for compounds **7f**,**g**,**o**, which were simply washed with $CHCl_3$ (3 × 10 mL).

***N*^{1},*N*^{4}-Diphenethylbut-2-ynediamide (7a)**

Following the general procedure, workup B yielded **7a** (1.17 g, 73%) as a colorless solid; mp 151 °C (CH_2Cl_2–PE).

IR (KBr): 3280, 3062, 2256, 1635, 1539 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.16 (m, 10 H), 6.31 (t, *J* = 6.8 Hz, 2 H), 3.59 (dt, *J* = 7.0, 6.8 Hz, 4 H), 2.86 (t, *J* = 7.0 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.70, 138.15, 128.74, 128.68, 126.73, 76.69, 41.21, 34.93.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{20}N_2O_2$: 320.1525; found: 320.1527.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.99; H, 6.24; N, 8.75.

***N*^{1},*N*^{4}-Dipropylbut-2-ynediamide (7b)**

Following the general procedure, workup A yielded **7b** (0.58 g, 59%) as a colorless solid; mp 149 °C (CH_2Cl_2–PE) (Lit.[5] 151–153 °C).

IR (KBr): 3296, 3059, 2971, 2874, 1636, 1548, 1319, 1288, 1153 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (t, *J* = 5.4 Hz, 2 H), 3.25 (dt, *J* = 6.9, 5.4 Hz, 4 H), 1.58–1.54 (m, 4 H), 0.93 (t, *J* = 7.4 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.94, 76.79, 41.78, 22.26, 11.27.

MS (EI): *m*/*z* = 195.1 $[M]^+$.

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 60.93; H, 8.17; N, 14.12.

***N*^{1},*N*^{4}-Dibutylbut-2-ynediamide (7c)**

Following the general procedure, workup A yielded **7c** (0.71 g, 63%) as a colorless solid; mp 142 °C (CH_2Cl_2–PE).

IR (KBr): 3285, 3059, 2960, 2868, 1638, 1544, 1291 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 5.5 Hz, 2 H), 3.29 (dt, *J* = 7.1, 5.5 Hz, 4 H), 1.61–1.47 (m, 4 H), 1.39–1.32 (m, 4 H), 0.92 (t, *J* = 7.4 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.87, 76.75, 39.80, 30.97, 19.95, 13.58.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{20}N_2O_2$: 224.1525; found: 224.1501.

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.27; H, 8.99; N, 12.36.

***N*^{1},*N*^{4}-Dihexylbut-2-ynediamide (7d)**

Following the general procedure, workup A yielded **7d** (0.94 g, 67%) as a colorless solid; mp 140 °C (CH_2Cl_2–PE).

IR (KBr): 3295, 2960, 1628, 1309, 1276 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 5.7 Hz, 2 H), 3.36–3.24 (m, 4 H), 1.56–1.50 (m, 4 H), 1.36–1.27 (m, 12 H), 0.89 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.80, 76.69, 40.13, 31.36, 28.94, 26.49, 22.50, 13.96.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{28}N_2O_2$: 280.2151; found: 280.2140.

Anal. Calcd for $C_{16}H_{28}N_2O_2$: C, 68.53; H, 10.06; N, 9.99. Found: C, 68.37; H, 9.83; N, 9.75.

***N*^{1},*N*^{4}-Diallylbut-2-ynediamide (7e)**

Following the general procedure, workup A yielded **7e** (0.60 g, 62%) as a colorless solid; mp 105 °C (CH_2Cl_2–PE) (Lit.[5] 103–104 °C).

IR (KBr): 3274, 3054, 1636, 1538, 1282 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (s, 2 H), 5.83–5.78 (m, 2 H), 5.24–5.15 (m, 4 H), 3.92– (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.70, 132.55, 117.22, 76.82, 42.31.

MS (EI): *m*/*z* = 192.1 $[M]^+$.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.21; H, 6.26; N, 14.52.

***N*^{1},*N*^{4}-Di(prop-2-ynyl)but-2-ynediamide (7f)**

Following the general procedure, workup B yielded **7g** (0.75 g, 80%) as a colorless solid; mp 151 °C (EtOH).

IR (KBr): 3288, 3043, 1633, 1528, 1280 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.50 (d, *J* = 5.4 Hz, 2 H), 3.94 (dd, *J* = 5.4, 2.2 Hz, 4 H), 3.16 (t, *J* = 2.2 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 150.92, 80.19, 77.03, 73.99, 28.73.

MS (EI): *m*/*z* = 188.1 $[M]^+$.

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.47; H, 4.31; N, 14.60.

***N*^{1},*N*^{4}-Dibenzylbut-2-ynediamide (7g)**

Following the general procedure, workup B yielded **7g** (1.05 g, 72%) as a colorless solid; mp 203 °C (EtOH) (Lit.[5] 204–205 °C).

IR (KBr): 3219, 3055, 2932, 1634, 1558 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.56 (t, *J* = 6.0 Hz, 2 H), 7.36–7-26 (m, 10 H), 4.35 (d, *J* = 6.0 Hz, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.32, 138.64, 128.86, 127.83, 127.57, 77.32, 42.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{16}N_2O_2$: 292.1212; found: 292.1216.

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.94; H, 5.46; N, 9.59.

N^1,N^4-Bis(1,3-benzodioxol-5-ylmethyl)but-2-ynediamide (7h)
Following the general procedure, workup B yielded **7h** (1.27 g, 67%) as a pale yellow solid; mp 223 °C (MEK).

IR (KBr): 3263, 3071, 2898, 2785, 1850, 1630, 1551, 1493, 1466 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.46 (t, *J* = 6.0 Hz, 2 H), 6.86 (d, *J* = 7.9 Hz, 2 H), 6.82 (d, *J* = 1.4 Hz, 2 H), 6.74 (dd, *J* = 7.9, 1.4 Hz, 2 H), 5.99 (s, 4 H), 4.24 (d, *J* = 6.0 Hz, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.22, 147.74, 146.78, 132.46, 121.20, 108.54, 108.49, 101.37, 77.30, 42.75.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{16}N_2O_6$: 380.1008; found: 380.0996.

Anal. Calcd for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.42; N, 7.37. Found: C, 62.93; H, 4.31; N, 7.36.

N^1,N^4-Dicyclohexylbut-2-ynediamide (7i)
Following the general procedure, workup B yielded **7i** (0.94 g, 68%) as a colorless solid; mp 235 °C dec. (CH_2Cl_2–PE) (Lit.[5] 244–245 °C).

IR (KBr): 3300, 2936, 2858, 1636, 1524, 1321 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.89 (d, *J* = 7.9 Hz, 2 H), 3.71–3.50 (m, 2 H), 1.83–1.62 (m, 8 H), 1.55 (dd, *J* = 9.3, 3.5 Hz, 2 H), 1.38–0.95 (m, 10 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 150.40, 77.19, 48.70, 32.31, 25.47, 24.89.

MS (EI): *m*/*z* = 276.2 [M]$^+$.

Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.72; H, 8.59; N, 10.02.

N^1,N^4-Bis[(*R*)-1-phenylethyl]but-2-ynediamide (7j)
Following the general procedure, workup B yielded **7j** (1.12 g, 70%) as a colorless solid, which was recrystallized (CH_2Cl_2–PE); mp 172 °C dec.

IR (KBr): 3297, 2937, 1640, 1527, 1270 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66–7.12 (m, 12 H), 5.08 (m, 2 H), 1.49 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.76, 141.96, 128.72, 127.64, 126.19, 76.80, 49.77, 21.47.

MS (EI): *m*/*z* = 320.1 [M]$^+$.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.64; H, 6.28; N, 8.55.

N^1,N^4-Diphenylbut-2-ynediamide (7k)
Following the general procedure, workup A yielded **7k** (0.71 g, 54%) as a pale yellow solid; mp 185 °C dec. (MeOH).

IR (KBr): 3280, 1641, 1527, 1445, 1325, 1264 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.21 (s, 2 H), 7.64 (d, *J* = 7.8 Hz, 4 H), 7.36 (dd, *J* = 7.8, 7.3 Hz, 4 H), 7.14 (d, *J* = 7.3 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 149.18, 138.37, 129.41, 125.14, 120.34, 77.89.

MS (EI): *m*/*z* = 264.3 [M]$^+$.

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.47; H, 4.59; N, 10.52.

N^1,N^4-Bis(4-methoxyphenyl)but-2-ynediamide (7l)
Following the general procedure, workup B yielded **7l** (0.99 g, 61%) as a greenish solid; mp 210 °C dec. (MeOH).

IR (KBr): 3271, 1640, 1598, 1510, 1244 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.05 (s, 2 H), 7.55 (d, *J* = 8.9 Hz, 4 H), 6.92 (d, *J* = 8.9 Hz, 4 H), 3.73 (s, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.59, 148.79, 131.52, 121.83, 114.51, 77.91, 55.67.

MS (EI): *m*/*z* = 324.3 [M]$^+$.

Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.54; H, 4.95; N, 8.62.

N^1,N^1,N^4,N^4-Tetrabutylbut-2-ynediamide (7m)
Following the general procedure, workup A yielded **7m** (1.12 g, 67%) as a colorless oil.

IR (KBr): 3258, 2931, 2874, 1633 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.51 (t, *J* = 7.4 Hz, 2 H), 3.35 (t, *J* = 7.6 Hz, 2 H), 1.62–1.48 (m, 4 H), 1.39–1.26 (m, 4 H), 0.94 (t, *J* = 7.4 Hz, 3 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.59, 80.86, 48.72, 44.51, 30.95, 29.32, 20.11, 19.84, 13.73, 13.72.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{36}N_2O_2$: 336.2777; found: 336.2734.

Anal. Calcd for $C_{20}H_{36}N_2O_2$: C, 71.38; H, 10.78; N, 8.32. Found: C, 71.31; H, 10.61; N, 8.10.

N^1,N^1,N^4,N^4-Tetrallylbut-2-ynediamide (7n)
Following the general procedure, workup A yielded **7n** (0.712 g, 52%) as a colorless oil.

IR (KBr): 3084, 2985, 2926, 1634, 1416, 1247 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.97–5.58 (m, 4 H), 5.45–5.05 (m, 8 H), 4.13 (d, *J* = 5.6 Hz, 4 H), 4.01 (d, *J* = 6.0 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.47, 132.18, 131.49, 118.51, 118.48, 80.43, 50.52, 46.55.

MS (EI): *m*/*z* = 272.1 [M]$^+$.

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.24; H, 7.40; N, 10.15.

N^1,N^1,N^4,N^4-Tetrabenzylbut-2-ynediamide (7o)
Following the general procedure, workup B yielded **7o** (1.63 g, 69%) as a colorless solid; mp 134 °C (EtOH).

IR (KBr): 3025, 2932, 1636, 1451, 1423 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.41–7.25 (m, 12 H), 7.24–7.11 (m, 8 H), 4.59 (s, 4 H), 4.47 (s, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.81, 136.37, 136.30, 129.20, 129.05, 128.30, 128.19, 127.96, 127.58, 81.21, 51.80, 47.66.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{32}H_{28}N_2O_2$: 472.2151; found: 472.2121.

Anal. Calcd for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 80.97; H, 5.93; N, 5.87.

1,4-Di(pyrrolidin-1-yl)but-2-yne-1,4-dione (7q)
Following the general procedure, workup A yielded **7q** (0.64 g, 58%) as a colorless solid; mp 118 °C (CH_2Cl_2–PE) (Lit.[5] 118–119 °C).

IR (KBr): 2956, 2884, 1624, 1457, 1427 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.65 (dd, *J* = 9.8, 3.7 Hz, 2 H), 3.47 (dd, *J* = 9.8, 3.7 Hz, 2 H), 1.95–1.90 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.73, 80.02, 48.07, 45.48, 25.27, 24.50.

MS (EI): m/z = 220.2 $[M]^+$.

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.24; H, 7.28; N, 12.53.

N^1,N^4-Dibenzyl-N^1,N^4-dimethylbut-2-ynediamide (7r)
Following the general procedure, workup B yielded **7r** (1.01 g, 63%) as a colorless solid; mp 127 °C (CH_2Cl_2–PE).

IR (KBr): 1634, 1404, 1239 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.15 (m, 10 H), 4.80, 4.73, 4.64 and 4.61 (4 s, 4 H), 3.16, 3.08, 2.93 and 2.91 (4 s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.90, 152.81, 152.77, 152.67, 135.58, 135.44, 135.33, 128.96, 128.93, 128.79, 128.26, 128.15, 128.09, 127.89, 127.37, 127.28, 81.39, 81.34, 81.02, 80.89, 54.80, 54.69, 50.02, 35.77, 35.62, 32.10, 32.06.

MS (EI): m/z = 320.1 $[M]^+$.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.73; H, 6.25; N, 8.65.

Diethyl 2,2′-[(But-2-ynedioyl)bis(azanediyl)]diacetate (7s)
Following the general procedure, workup A yielded **7s** (0.91 g, 64%) as a colorless solid; mp 121 °C (CH_2Cl_2–PE).

IR (KBr): 3378, 3289, 2992, 1756, 1659, 1527 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.55 (s, 2 H), 4.24 (q, J = 7.1 Hz, 4 H), 4.11 (d, J = 5.6 Hz, 4 H), 1.30 (t, J = 7.1 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.03, 151.74, 76.99, 61.92, 41.50, 14.07.

MS (ESI): m/z = 307.2 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.85; H, 5.64; N, 9.97.

Dimethyl 2,2′-[(But-2-ynedioyl)bis(azanediyl)]bis(4-methylpentanoate) (7t)
Following the general procedure, workup A yielded **7t** (1.30 g, 71%) as a colorless solid; mp 88 °C (CH_2Cl_2–PE).

IR (KBr): 3479, 3297, 2960, 1758, 1645, 1558 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.3 Hz, 2 H), 4.65 (dt, J = 8.3, 5.4 Hz, 2 H,), 3.76 (s, 6 H), 1.87–1.55 (m, 6 H), 0.95 (d, J = 6.4 Hz, 6 H), 0.94 (d, J = 6.4 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.26, 151.90, 77.37, 52.69, 51.34, 40.86, 24.93, 22.85, 21.74.

MS (ESI): m/z = 391.3 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{28}N_2O_6$: C, 58.68; H, 7.66; N, 7.60. Found: C, 58.39; H, 7.61; N, 7.51.

Dimethyl 2,2′-[(But-2-ynedioyl)bis(azanediyl)]bis(3-phenylpropanoate) (7u)
Following the general procedure, workup A yielded **7u** (1.42 g, 65%) as a colorless solid; mp 142 °C (CH_2Cl_2–PE).

IR (KBr): 3301, 2953, 1740, 1652, 1538, 1439, 1285 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 8 H), 7.20–7.13 (m, 4 H), 4.90 (td, J = 7.3, 5.7 Hz, 2 H), 3.76 (s, 6 H), 3.17 (d, J = 14.0, 5.7 Hz, 2 H), 3.06 (d, J = 14.0, 7.3 Hz, 2 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.37, 151.21, 135.31, 129.17, 128.73, 127.34, 76.87, 53.91, 52.63, 37.52.

MS (ESI): m/z = 459.3 $[M + Na]^+$.

Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.00; H, 5.51; N, 6.31.

Dimethyl 2,2′-[(but-2-ynedioyl)bis(azanediyl)]bis(2-phenylacetate) (7v)
Following the general procedure, workup B yielded **7v** (1.51 g, 69%) as a colorless solid; mp 164 °C (CH_2Cl_2–PE).

IR (KBr): 3301, 3064, 2953, 1740, 1652, 1538, 1439, 1285 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.7 Hz, 2 H), 7.42–7.33 (m, 10 H), 5.71 (d, J = 7.7 Hz, 2 H), 3.76 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.68, 150.67, 135.10, 129.11, 128.91, 127.37, 76.93, 56.65, 53.11.

HRMS (EI): m/z $[M]^+$ calcd for $C_{22}H_{20}N_2O_6$: 408.1321; found: 408.1344.

Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.64; H, 4.93; N, 6.71.

N^1,N^4-Bis[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]-N^1,N^4-dimethylbut-2-ynediamide (7w)
Following the general procedure, workup B yielded **7w** (1.33 g, 65%) as a colorless solid; mp 82 °C (CH_2Cl_2–PE).

IR (KBr): 3420, 2938, 1622, 1404 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 10 H), 4.94, 4.92, 4.73, and 4.77 (4 d, J = 8.0/8.0/7.9/6.3 Hz, resp., total 2 H), 4.61–4.45 (m, 2 H), 3.33 (br s, 2 H), 3.09, 3.03, 2.86, and 2.86 (4 s, 6 H), 1.32, 1.27, 1.22, and 1.20 (4 d, J = 6.8/6.8/7.1/7.1 Hz, resp., total 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.54, 152.93, 152.82, 141.45, 141.43, 141.15, 140.92, 128.51, 128.36, 128.11, 127.98, 127.75, 126.25, 126.06, 81.66, 81.51, 81.46, 81.38, 76.92, 76.61, 75.94, 59.96, 59.79, 56.90, 56.73, 34.05, 33.98, 28.75, 28.46, 13.53, 13.04, 11.03, 10.94.

MS (EI): m/z = 408.2 $[M]^+$.

Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.37; H, 6.96; N, 6.68.

N^1,N^4-Bis{3-[5-(dimethylamino)naphthalene-1-sulfonamido]propyl}but-2-ynediamide (7x)
Following the general procedure, workup B yielded **7x** (2.11 g, 61%) as a yellow solid; mp 97 °C (CH_2Cl_2–PE).

^1H NMR (500 MHz, DMSO-d_6): δ = 8.91 (t, J = 5.7 Hz, 2 H), 8.48 (d, J = 8.5 Hz, 2 H), 8.32 (d, J = 8.5 Hz, 2 H), 8.12 (dd, J = 7.1, 1.2 Hz, 2 H), 7.90 (t, J = 5.7 Hz, 2 H), 7.65–7.61 (m, 4 H), 7.27 (d, J = 7.1 Hz, 2 H), 3.10–3.04 (m, 4 H), 2.84 (s, 12 H), 2.82–2.78 (m, 4 H), 1.58–1.51 (m, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 151.86, 151.22, 136.44, 129.88, 129.58, 128.66, 128.30, 124.03, 119.53, 115.59, 76.97, 45.53, 40.76, 37.10, 29.47.

MS (EI): m/z = 692.3 $[M]^+$.

Anal. Calcd for $C_{34}H_{40}N_6O_6S_2$: C, 58.94; H, 5.82; N, 12.13. Found: C, 59.12; H, 5.68; N, 11.79.

N^1,N^4-Bis(*N*-{2-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)oxy]ethyl})but-2-ynediamide (7y)
Following the general procedure, workup A yielded **7y** (2.54 g, 59%) as a colorless solid, which was recrystallized (CH_2Cl_2–PE); mp 105 °C.

IR (KBr): 3349, 2960, 1753, 1668, 1538, 1373, 1227 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.73 (t, J = 5.7 Hz, 2 H), 5.40 (dd, J = 3.4, 1.0 Hz, 2 H), 5.22–5.15 (m, 2 H), 5.03 (dd, J = 10.3, 3.4 Hz, 2 H), 4.50 (d, J = 7.9 Hz, 2 H), 4.20 (dd, J = 11.3, 6.7 Hz, 2 H), 4.14 (dd, J = 11.3, 6.5 Hz, 2 H), 3.95 (dt, J = 6.6, 1.0 Hz, 2 H), 3.88 (ddd, J = 10.3, 6.3, 4.0 Hz, 2 H), 3.76 (ddd, J = 10.3, 6.3, 4.0 Hz, 2 H), 3.58–3.45 (m, 4 H), 2.17 (s, 6 H), 2.09 (s, 6 H), 2.06 (s, 6 H), 1.99 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.46, 170.13, 169.99, 169.69, 151.19, 101.30, 76.43, 70.91, 70.72, 68.75, 68.09, 66.97, 61.37, 39.73, 20.77, 20.63, 20.60, 20.50.

MS (EI): m/z = 860.4 $[M]^+$.

Anal. Calcd for $C_{36}H_{48}N_2O_{22}$: C, 50.23; H, 5.62; N, 3.25. Found: C, 50.51; H, 5.95; N, 2.95.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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