Short Communication

Synthesis of 3-[(2-Amino-1,2-dicyanovinyl)amino]-2-(benzoylamino)propenoates

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Abstract

Two simple methods for the preparation of 3-[(2-amino-1,2-dicyanovinyl)amino]-2-(benzoylamino)propenoates starting from 4-ethoxymethylidene-2-phenyl-5(4*H*)-oxazolone and diaminomaleonitrile are described.

Key words: diaminomaleonitrile, 5(4*H*)-oxazolones, propenoates

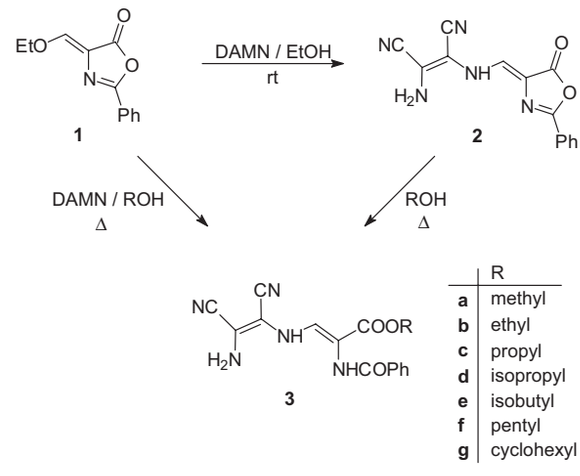
Introduction

Diaminomaleonitrile (DAMN) is an excellent synthetic tool for the preparation of highly substituted imidazoles, pyrimidines, pyrazines, purines, diazepines, pyrroles and other heterocycles.[1,2] These syntheses are usually carried out via *N*-substituted DAMN derivatives such as, for example, *N*-(2-amino-1,2-dicyanovinyl) substituted formimidates, formamidines, formamidrazones, carboxamides, formamide *O*-alkyloximes and Schiff bases. During the course of our investigations on the use of DAMN in heterocyclic synthesis, we designed new approaches to 1,2,3-triazolyl substituted amino acid derivatives,[3] imidazo[1,5-*a*]pyrazines,[4] [1,2,3]triazolo[1,5-*a*]pyrazines,[5] and [1,2,3]triazolo[1,5-*a*][1,2,4]triazolo[5,1-*c*]pyrazines.[6] In some of these cases, new DAMN derivatives, alkyl 3-[(2-amino-1,2-dicyanovinyl)amino]-2-(benzoylamino)propenoates, were used as the key intermediates. Since until now the preparation and characterization of the above stated propenoates have been mentioned only briefly, we give herein a report on these compounds in more detail.

Results and discussion

We have elaborated two simple general methods for the preparation of the propenoates **3** starting from the oxazolones **1** and **2** (Scheme 1, Table 1).

In the first one-pot approach, a mixture of 4-ethoxymethylidene-2-phenyl-5(4*H*)-oxazolone **1**,[7] DAMN and the corresponding alcohol was heated under reflux to give the propenoates **3a–g** in 23–82 % isolated yield. In the second approach, the *N*-substituted DAMN **2**[3] was heated in the corresponding alcohol



Scheme 1. Synthesis of the propenoates **3a–g**.

Table 1. Reaction times and yields in the synthesis of the propenoates **3a–g**.

R	Product	From **1**		From **2**	
		Time	Yield[a]	Time	Yield[a, 4]
Methyl	**3a**	30 h	71	10 h	72
Ethyl	**3b**	9 h	82 (73[3])	6 h	79
Propyl	**3c**	1.5 h	55	1.5 h	71
Isopropyl	**3d**	23 h	35	8.5 h	58
Isobutyl	**3e**	2.5 h	23	50 min	70
Pentyl	**3f**	5 min	37	11 min	68
Cyclohexyl	**3g**	6 min	26	2 min	51

[a] Refers to isolated percent yield.

under reflux to afford the propenoates **3a–g** in 51–79 % isolated yield. In order to avoid possible side transformations of these multifunctional starting compounds and products, and to obtain sufficiently pure products without any additional purification, the reactions were performed in the absence of acid or base catalysts.

As evident from Table 1, the first one-pot procedure with **1** gave in most cases lower yields than the oxazolone ring opening of **2** probably due to the decomposition of DAMN at higher temperatures. The shortest reaction times were observed in both procedures with alcohols having much higher boiling points (pentyl alcohol, cyclohexyl alcohol).

The propenoates **3** have *Z*,*Z* configuration on the carbon-carbon double bonds in the vinylaminopropenoate unit. It is known that DAMN (*Z* isomer) is more stable than diaminofumaronitrile (*E* isomer) and that during the *N*-substitution reactions carried out on one amino group of DAMN the configurational integrity is maintained.[1,2] The *Z* configuration in the propenoate unit was established on the basis of the magnitude of the long-range heteronuclear coupling constant between the carbonyl carbon and the methylidene proton for **3c** ($^3J_{C-H}$ = 3 Hz) measured from the antiphase splitting of cross peaks in the HMBC spectrum. 2D NMR spectroscopy was also used for the partial assignment of ^{13}C signals for **3b**.

Experimental

Melting points were determined on a Kofler micro hot stage and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer with TMS as an internal standard. Elemental analyses for C,H,N were obtained on a Perkin-Elmer CHN Analyzer 2400. IR spectra were recorded on a Perkin-Elmer 1310 or 727 B spectrophotometer. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Compounds **1**[7] and **2**[3] were prepared as described in the literature. All other compounds were used without purification as obtained from commercial sources.

General procedure for the preparation of the propenoates 3 from 1. A mixture of the oxazolone **1** (1 mmol), DAMN (1 mmol), and the corresponding alcohol (3 mL) was heated under reflux until the starting compounds disappeared (TLC monitoring). In the case of **3b** the reaction was carried out with 10 mmol of the oxazolone **1** and DAMN in 75 mL of ethanol. After cooling, the precipitated **3** was filtered off and washed with a small amount of the applied alcohol or ethanol.

General procedure for the preparation of the propenoates 3 from 2. A mixture of the oxazolone **2** (3 mmol in the cases of **3a**, **3f**, and **3g**; 2 mmol in the cases of **3b**, **3c**, **3d**, and **3e**) and the corresponding alcohol (30 mL in the cases of **3a–f**; 10 mL in the case of **3g**) was heated under reflux until the starting compound disappeared (TLC monitoring). After cooling, the precipitated propenoate **3** was filtered off and washed with a small amount of the applied alcohol or ethanol.

Methyl (2*Z*)-3-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}-2-(benzoylamino)propenoate (3a). mp 209–210 °C (EtOH). IR (KBr) ν 3350, 3320, 3190, 2220, 2190, 1630, 1610, 1455, 1430, 1250, 700 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.63 (s, 3H, OCH_3), 6.97 (s, 2H, NH_2), 7.38 (d, *J* 12.2 Hz, 1H, H-3), 7.53 (m, 3H, H-3'', H-4'', H-5''), 7.95 (m, 3H, H-2'', H-6'', NH), 9.21 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 51.3, 96.9, 103.5, 114.8, 115.8, 118.7, 127.9, 128.2, 131.5, 134.0, 137.1, 165.3, 165.4. MS *m*/*z* (relative intensity): 311 (M^+, 17). Anal. Calcd for $C_{15}H_{13}N_5O_3$: C 57.87, H 4.21, N 22.50. Found: C 58.19, H 4.05, N 22.56.

Ethyl (2*Z*)-3-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}-2-(benzoylamino)propenoate (3b). mp 215–216 °C (EtOH) (lit.[3] 212.5–214.5 °C). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.3 (CH_3), 59.7 (OCH_2), 96.9 (C-1'), 103.7 (C-2), 114.7 (CN), 115.8 (CN), 118.7 (C-2'), 127.8 (C-2'', C-6''), 128.1 (C-3'', C-5''), 131.4 (C-4''), 134.0 (C-1''), 136.8 (C-3), 164.8 (C-1), 165.3 (NHCO). MS *m*/*z* (relative intensity): 325 (M^+, 15).

Propyl (2*Z*)-3-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}-2-(benzoylamino)propenoate (3c). mp 200–202 °C (PrOH). IR (KBr) ν 3370, 3350, 3200, 2220, 2200, 1630, 1610, 1570, 1495, 1465, 1375, 1360, 1255, 1150, 705 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, *J* 7.1 Hz, 3H, CH_3), 1.58 (tq, *J* 6.8, 7.1 Hz, 2H, $OCH_2\underline{CH_2}$,), 4.01 (t, *J* 6.8 Hz, 2H, OCH_2), 6.95 (s, 2H, NH_2), 7.39 (d, *J* 12.0 Hz, 1H, H-3), 7.53 (m, 3H, H-3'', H-4'', H-5''), 7.95 (m, 3H, H-2'', H-6'', NH), 9.19 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 10.3, 21.7, 65.1, 97.0, 103.7, 114.8, 115.7, 118.3, 127.8, 128.1, 131.4, 134.1, 136.7, 164.9, 165.4. MS *m*/*z* (relative intensity): 339 (M^+, 16). Anal. Calcd for $C_{17}H_{17}N_5O_3$: C 60.17, H 5.05, N 20.64. Found: C 60.19, H 5.23, N 20.35.

Isopropyl (2*Z*)-3-{[(*Z*)-2-amino-1,2-dicyano vinyl]amino}-2-(benzoylamino)propenoate (3d). mp 196–197 °C (i-PrOH). IR (KBr) ν 3380, 3350, 3200, 2220, 2210, 1650, 1610, 1500, 1465, 1365, 1255, 1100, 705 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21 (d, *J* 6.2 Hz, 6H, $2CH_3$), 4.91 (septet, *J* 6.2 Hz, 1H, OCH), 6.96 (s, 2H, NH_2), 7.34 (d, *J* 12.2 Hz, 1H, H-3), 7.52 (m, 3H, H-3'', H-4'', H-5''), 7.88 (d, *J* 12.2 Hz, 1H, NH), 7.96 (m, 2H, H-2'', H-6''), 9.16 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.8, 66.9, 96.9, 104.1, 114.8, 115.8, 118.6, 127.8, 128.1, 131.4, 134.1, 136.5, 164.4, 165.3. MS-FAB *m*/*z* (relative intensity): 340 (MH^+, 12). Anal. Calcd for $C_{17}H_{17}N_5O_3$: C 60.17, H 5.05, N 20.64. Found: C 60.31, H 5.04, N 20.67.

Isobutyl (2*Z*)-3-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}-2-(benzoylamino)propenoate (3e). mp 201–203 °C (i-BuOH). IR (KBr) ν 3370, 3350, 3200,

2220, 2200, 1635, 1610, 1460, 1365, 1255, 1150, 700 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 0.88 (d, *J* 6.4 Hz, 6H, $2CH_3$), 1.86 (m, 1H, $OCH_2\underline{CH}$), 3.84 (d, *J* 6.4 Hz, 2H, OCH_2), 6.94 (s, 2H, NH_2), 7.42 (d, *J* 12.0 Hz, 1H, H-3), 7.53 (m, 3H, H-3'', H-4'', H-5''), 7.97 (m, 3H, H-2'', H-6'', NH), 9.18 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 18.9, 27.5, 69.5, 97.1, 103.7, 114.8, 115.7, 118.0, 127.8, 128.1, 131.4, 134.1, 136.7, 164.8, 165.5. MS *m/z* (relative intensity): 353 (M^+, 17). Anal. Calcd for $C_{18}H_{19}N_5O_3$: C 61.18, H 5.42, N 19.82. Found: C 60.80, H 5.69, N 19.43.

Pentyl (2*Z*)-3-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}-2-(benzoylamino)propenoate (3f). mp 186–187 °C (EtOH). IR (KBr) ν 3370, 3330, 3200, 2220, 2200, 1635, 1610, 1465, 1375, 1255, 1150, 705 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (t, *J* 7.0 Hz, 3H, CH_3), 1.28 (m, 4H, $2CH_2$), 1.55 (m, 2H, $OCH_2\underline{CH_2}$), 4.04 (t, *J* 6.4 Hz, 2H, $O\underline{CH_2}$), 6.95 (s, 2H, NH_2), 7.38 (d, *J* 12.3 Hz, 1H, C-3), 7.53 (m, 3H, H-3'', H-4'', H-5''), 7.95 (m, 3H, H-2'', H-6'', NH), 9.18 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.8, 21.7, 27.6, 28.0, 63.6, 97.1, 103.7, 114.8, 115.7, 118.2, 127.8, 128.1, 131.4, 134.1, 136.7, 164.9, 165.4. MS *m/z* (relative intensity): 367 (M^+, 17). Anal. Calcd for $C_{19}H_{21}N_5O_3$: C 62.11, H 5.76, N 19.06. Found: C 62.07, H 5.79, N 19.12.

Cyclohexyl (2*Z*)-3-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}-2-(benzoylamino)propenoate (3g). mp 182–183 °C (EtOH). IR (KBr) ν 3380, 3340, 3200, 2920, 2230, 2210, 1655, 1615, 1505, 1475, 1365, 1255, 705 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 1.0–1.8 (m, 10H, cyclohexyl), 4.73 (m, 1H, cyclohexyl), 6.94 (s, 2H, NH_2), 7.39 (d, *J* 12.1 Hz, 1H, H-3), 7.53 (m, 3H, H-3'', H-4'', H-5''), 7.94 (m, 3H, H-2'', H-6'', NH), 9.16 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.7, 25.0, 31.0, 71.1, 97.1, 104.1, 114.8, 115.7, 118.1, 127.8, 128.1, 131.4, 134.2, 136.5, 164.2, 165.5. MS *m/z* (relative intensity): 379 (M^+, 8). Anal. Calcd for $C_{20}H_{21}N_5O_3$: C 63.31, H 5.58, N 18.46. Found: C 63.20, H 5.57, N 18.46.

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References

1. A. W. Erian, *Chem. Rev*. **1993**, *93*, 1991–2005, and references cited therein.
2. A. Al-Azmi, A.-Z. A. Elassar, B. L. Booth, *Tetrahedron* **2003**, *59*, 2749–2763, and references cited therein.
3. M. Polak, B. Verček, *Synth. Commun*. **2000**, *30*, 2863–2871.
4. T. Trček, A. Meden, B. Verček, *Synlett* **2000**, 1458–1460.
5. T. Jug, M. Polak, T. Trček, B. Verček, *Heterocycles* **2002**, *56*, 353–360.
6. T. Trček, B. Verček, *ARKIVOC* **2003**, *Part xiv*, 246–252.
7. J. W. Cornforth, *The Chemistry of Penicillin*; Princeton University Press, Princeton, 1949, p 803.

Povzetek

Opisani sta dve enostavni splošni metodi za pripravo 3-[(2-amino-1,2-dicianovinil)amino]-2-(benzoilamino)propenoatov iz 4-etoksimetiliden-2-fenil-5(4*H*)-oksazolona in diaminomaleonitrila (DAMN).