One-Pot Synthesis of Pentaalkyl 7-[(Alkylamino)carbonyl]-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4,5,6,7-pentacarboxylate

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Dedicated to Professor *Abdol J. Mostashari* on the occasion of his 65th birthday

Dialkyl acetylenedicarboxylates react with alkyl 2-nitroethanoates in the presence of alkyl isocyanides in a one-pot reaction to afford the title compounds in 78–90% yield.

Introduction. – Isocyanides are compounds with an extraordinary functional group; its unusual valence structure and reactivity have been discussed for more than 150 years [1–3]. Isocyanides are the only class of stable organic compounds with a formally divalent C-atom. Owing to its reactivity, the isocyanide group differs fundamentally from other functional groups. One of the classic applications in the chemistry of isocyanides is heterocyclic synthesis [3–6].

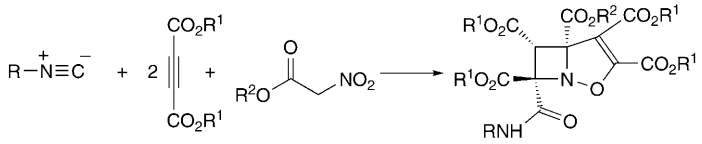
Multi-component reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention in the context of combinatorial chemistry. Of pivotal importance in this area are the isocyanide-based MCRs such as the versatile *Ugi* and *Passerini* reactions [1–4]. MCRs have been used to create diversity-oriented and biased combinatorial libraries, and for the synthesis of highly complex natural products.

As part of our current studies on the development of new routes in heterocyclic synthesis [7], we now report an efficient one-pot synthesis of pentaalkyl 7-[(alkylamino)-carbonyl]-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4,5,6,7-pentacarboxylates **1**.

Results and Discussion. – The reaction of the acetylenic esters **2** with the alkyl 2-nitroethanoates **3** in the presence of the alkyl isocyanides **4** in CH_2Cl_2 proceeded smoothly at ambient temperature to afford the target compounds **1** in 78–90% yield (based on the isocyanide; *Scheme 1*). The structures of compounds **1a**–**e** were confirmed by elemental analysis, IR, ^{1}H-NMR, and ^{13}C-NMR experiments. Although the skeleton of **1** contains three stereogenic centers, according to the ^{1}H- and ^{13}C-NMR spectra of the reaction mixtures, only one diastereoisomer was observed (racemic mixtures).

According to the X-ray crystal-structure of **1a** (see below), the bulky (*tert*-butylamino)carbonyl group prefers the *exo* position of the rigid bicyclic skeleton. The CO_2R'' group and the lone pair of the bridgehead N-atom are *cis*-oriented, and the ester group on C(6) is in *exo* position. Thus, only one of the possible diastereoisomers was

Scheme 1



4	R
a	^{t}Bu
b	1,1,3,3-tetra-methylbutyl

2	R^1
a	Me
b	Et
c	^{t}Bu

3	R^2
a	Me
b	Et

1	R	R^1	R^2	Yield [%]
a	^{t}Bu	Me	Me	90
b	^{t}Bu	Et	Me	81
c	^{t}Bu	Me	Et	78
d	^{t}Bu	^{t}Bu	Et	84
e	1,1,3,3-tetra-methylbutyl	Me	Et	80

formed, (1*R*,5*S*,6*R*,7*S*)-**1** (and its enantiomer). The ^{1}H-NMR spectrum of **1a** exhibited seven sharp *singlets* readily recognized as arising from the *t*-Bu (δ(H) 1.35), MeO (δ(H) 3.68, 3.77, 3.78, 3.82, and 3.87), and methine (δ(H) 4.91) H-atoms, along with a fairly broad resonance at δ(H) 7.04 for the NH group. The ^{1}H-decoupled ^{13}C-NMR spectrum of **1a** showed 18 distinct signals, in agreement with the proposed structure.

Unambiguous evidence for the structure of **1a** was obtained by single-crystal X-ray analysis. An ORTEP [8] diagram of **1a** is shown in the *Figure*. There are four molecules of **1a** in the unit cell. Details of the structure determination and refinement are described in the *Exper. Part*.

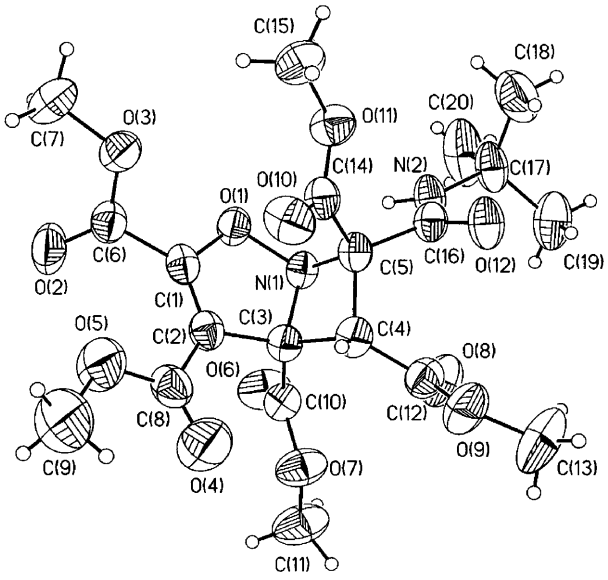
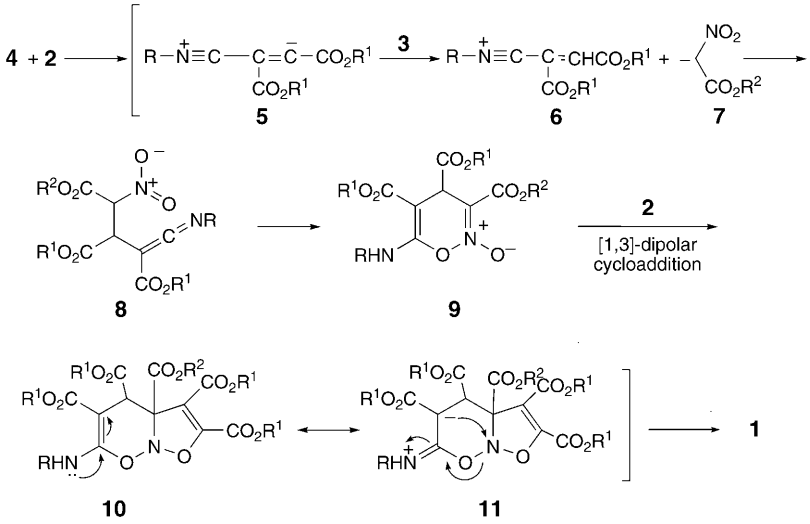


Figure. *X-Ray crystal structure of* **1a** (ORTEP-III plot [8]; arbitrary atom numbering)

Although the mechanistic details of the reaction are not known, a plausible pathway may be advanced to rationalize product formation (*Scheme 2*). Presumably, the zwitter-

Scheme 2



ionic intermediate **5**, formed from the isocyanide and the acetylenic ester, is protonated by **3** to furnish intermediate **6**, which is attacked by the anion of the CH-acidic **3** in a *Michael* fashion to produce ketenimine **8**. The latter then can undergo cyclization under the reaction conditions to afford the nitronic ester **9** [9]. Finally, 1,3-dipolar cycloaddition [10] between **9** and **2** leads to the oxazine derivative **10**, which rearranges to the heterocyclic system **1**.

In summary, the reaction between dialkyl acetylenedicarboxylates and alkyl 2-nitroethanoate in the presence of alkyl isocyanides provides a simple one-pot synthesis of pentaalkyl 7-[(alkylamino)carbonyl]-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4,5,6,7-pentacarboxylates of potential synthetic and pharmaceutical interest. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

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Experimental Part

General. Compounds **2**–**4** were obtained from *Fluka*, and were used without further purification. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-500 AVANCE* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp; δ in ppm, J in Hz. EI-MS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in m/z. Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **1**. To a stirred soln. of **2** (4 mmol) and **3** (0.26 g, 2 mmol) in anh. CH_2Cl_2 (10 ml) was added dropwise a mixture of **4** (2 mmol) in CH_2Cl_2 (5 ml) at $-5°$ over 10 min. The mixture was then allowed to warm to r.t., and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/AcOEt 4 : 1) to afford the pure title compounds.

Pentamethyl 7-[(tert-*Butylamino)carbonyl]-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4,5,6,7-pentacarboxylate* (**1a**). Yield: 0.86 g (90%). Pale-yellow powder. M.p. 164–166°. IR (KBr): 3390 (NH); 1746, 1736, 1724, 1716, 1705, 1685 (C=O); 1516; 1260. ^{1}H-NMR: 1.35 (*s*, Me_3C); 3.68, 3.77, 3.78, 3.82, 3.87 (5*s*, 5 MeO); 4.91 (*s*, CH); 7.04 (*s*, NH). ^{13}C-NMR: 28.2 (Me_3C); 51.2 (Me_3C); 51.8 (CH); 52.6, 52.7, 53.1, 53.6, 54.0 (5 MeO); 76.0, 76.7, 109.4 (3 C); 154.1 (C–O); 157.4, 160.2, 163.7, 164.8, 166.2, 167.4 (6 C=O). EI-MS: 486 (2, M^+), 427 (3), 328 (82), 296 (86), 268 (28), 252 (83), 211 (84), 171 (100), 156 (42), 115 (18), 105 (14), 59 (85), 57 (87), 41 (23). Anal. calc. for $C_{20}H_{26}N_2O_{12}$ (486.42): C 49.38, H 5.39, N 5.76; found: C 49.76, H 5.62, N 5.94.

3,4,6,7-Tetraethyl 5-Methyl 7-[(tert-*Butylamino)carbonyl]-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4,5,6,7-pentacarboxylate* (**1b**). Yield: 0.88 g (81%). Pale-yellow powder. M.p. 104–106°. IR (KBr): 3395 (NH); 1745, 1741, 1737, 1732, 1722, 1685 (6 C=O); 1515; 1253. ^{1}H-NMR: 1.26 (*t*, ^3J=7.2, Me); 1.27 (*t*, ^3J=7.2, Me); 1.28 (*t*, ^3J=7.2, Me); 1.34 (*t*, ^3J=7.2, Me); 1.37 (*s*, Me_3C); 3.78 (*s*, MeO); 4.10–4.40 (*m*, 4 CH_2O); 4.92 (*s*, CH); 7.08 (*s*, NH). ^{13}C-NMR: 13.7, 13.8, 13.9, 14.0 (4 Me); 28.3 (Me_3C); 51.3 (Me_3C); 51.7 (CH); 52.9 (MeO); 61.6, 61.9, 63.1, 63.4 (4 CH_2O); 76.1, 77, 109.4 (4 C); 154.0 (C–O); 157.1, 159.8, 164.0, 164.1, 166.4, 167.3 (6 C=O). EI-MS: 542 (1, M^+), 442 (6), 370 (25), 324 (26), 252 (100), 196 (17), 170 (16), 143 (28), 115 (12), 59 (18), 57 (59), 41 (16). Anal. calc. for $C_{24}H_{34}N_2O_{12}$ (542.53): C 53.13, H 6.32, N 5.16; found: C 53.46, H 6.11, N 5.74.

5-Ethyl 3,4,6,7-Tetramethyl 7-[(tert-*Butylamino)carbonyl]-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4,5,6,7-pentacarboxylate* (**1c**). Yield: 0.78 g (78%). Pale-yellow oil. IR (KBr): 3385 (NH); 1743 1730, 1721, 1715, 1706, 1678 (6 C=O); 1557; 1254. ^{1}H-NMR: 1.36 (*s*, Me_3C); 1.39 (*t*, ^3J=7.2, Me); 3.68, 3.78, 3.83, 3.88 (4*s*, 4 MeO); 4.31 (*q*, ^3J=7.2, CH_2O); 4.93 (*s*, CH); 7.11 (*s*, NH). ^{13}C-NMR: 13.8 (Me); 28.3 (Me_3C); 51.4 (Me_3C); 51.8 (CH); 52.6, 52.7, 53.6, 54.1 (4 MeO); 62.5 (CH_2O); 76.0, 76.8, 109.6 (3 C); 153.8 (C–O); 157.5, 160.4, 164.0, 164.9, 165.8, 167.3 (6 C=O). EI-MS: 500 (2, M^+), 443 (8), 428 (15), 400 (21), 374 (18), 342 (50), 282 (26), 185 (48), 105 (9), 59 (62), 57 (100), 41 (19). Anal. calc. for $C_{21}H_{28}N_2O_{12}$ (500.45): C 50.40, H 5.64, N 5.60; found: C 50.86, H 5.80, N 5.96.

*3,4,6,7-Tetra(*tert-*Butyl) 5-Ethyl 7-[(*tert-*Butylamino)carbonyl]-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4,5,6,7-pentacarboxylate* (**1d**). Yield: 1.12 g (84%). Pale-yellow oil. IR (KBr): 3380 (NH); 1740, 1732, 1722, 1712, 1707, 1679 (6 C=O); 1558; 1260. ^{1}H-NMR: 1.37 (*t*, ^3J=7.1, Me); 1.48, 1.49, 1.50, 1.51, 1.52 (5*s*, 5 Me_3C); 4.30 (*q*, ^3J=7.1, CH_2O); 4.86 (*s*, CH); 7.21 (*s*, NH). ^{13}C-NMR: 13.8 (Me); 27.5, 27.6, 27.7, 27.8, 27.9 (5 Me_3C); 51.5 (Me_3C); 52.2 (CH); 62.3 (CH_2O); 75.7, 79.9 (2 C); 82.0, 82.4, 83.9, 84.7 (4 Me_3C); 110.6 (C); 151.7 (C–O); 155.7, 159.2, 163.1, 164.7, 166.1, 166.7 (6 C=O). EI-MS: 668 (1, M^+), 611 (8), 599 (23), 567 (22), 498 (60), 439 (27), 338 (56), 284 (11), 101 (70), 59 (31), 57 (100), 41 (29). Anal. calc. for $C_{33}H_{52}N_2O_{12}$ (668.77): C 59.26, H 7.84, N 4.19; found: C 59.71, H 7.69, N 4.47.

5-Ethyl 3,4,6,7-Tetramethyl 7-[[(1,1,3,3-Tetramethylbutyl)amino]carbonyl]-2-oxa-1-azabicyclo[3.2.0]-hept-3-ene-3,4,5,6,7-pentacarboxylate (**1e**). Yield: 0.88 g (80%). Pale-yellow oil. IR (KBr): 3400 (NH); 1742, 1739, 1730, 1721, 1715, 1681 (6 C=O); 1517; 1256. ^{1}H-NMR: 1.15 (*s*, Me_3C); 1.35 (*t*, ^3J=7.2, Me); 1.52, 1.54 (2*s*, 2 Me); 1.61 (*d*, ^2J=15.0, CH); 1.88 (*d*, ^2J=15.0, CH); 3.78, 3.88, 3.91, 3.98 (4*s*, 4 MeO); 4.31–4.32 (*m*, CH_2O); 5.04 (*s*, CH); 7.41 (*s*, NH). ^{13}C-NMR: 13.9, 27.5, 28.2 (3 Me); 31.5. (Me_3-C); 31.6 (Me_3C); 51.4 (Me_2C); 52.5 (CH); 52.7, 53.6, 53.7, 53.9 (4 MeO); 55.3 (CH_2); 62.4 (CH_2O); 76.0, 76.6, 109.5 (3 C); 154.0 (C–O); 157.5, 160.4, 163.4, 164.9, 165.6, 167.4 (6 C=O). EI-MS: 556 (1, M^+), 400 (8), 497 (33), 485 (13), 443 (87), 428 (67), 369 (42), 357 (22), 128 (100), 113 (80), 71 (54), 59 (100), 57 (78), 42 (19). Anal. calc. for $C_{25}H_{36}N_2O_{12}$ (556.56): C 53.94, H 6.52, N 5.04; found: C 54.01, H 6.58, N 5.08.

X-Ray Crystal Structure of **1a**[1]). Structure-determination and refinement data: formula, $C_{20}H_{26}N_2O_{12}$, M_r 486.43; crystal size, 0.22×0.20×0.17 mm, crystal system, monoclinic, a=9.1177(6), b=9.7933(7), c=26.7605(18) Å, α=90, β=92.635(5), γ=90°; space group $P\ 2_1/c$; Z=4, V=2387.0(3) Å^3, $D_{calc.}$=1.354 g cm^{-3}; R=0.0473, R_w=0.0999; $-7 \le h \le 12$; $-12 \le k \le 12$; $-35 \le l \le 35$; MoK_α radiation (λ=0.71073 Å); T=273(2) K.

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[1]) The crystallographic data of **1a** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC-604100. Copies of the data can be obtained, free of charge, *via* the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44-1223-336033).

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