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Synthesis of substituted nortrop-2-enes and 3-vinylpyridin-2-ones via reaction of 1,2,3,4,5,6,7-heptamethoxycarbonylcycloheptatriene with primary amines

Yury V. Tomilov *, Dmitry N. Platonov, Galina P. Okonnishnikova

N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation

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ABSTRACT

The mode of reaction of the 1,2,3,4,5,6,7-heptamethoxycarbonylcycloheptatriene with primary amines depends on the reaction conditions and leads to selective formation of N-substituted (heptamethoxycarbonyl)nortrop-2-enes and/or 3-vinylpyridin-2-ones bearing six ester groups. The influence of the solvent on the selectivity of the formation of nortropenes and pyridinones was studied.

Previously we have shown[1] that the reaction of methyl diazoacetate with dimethyl dibromosuccinate in pyridine gives cycloheptatriene-1,2,3,4,5,6,7-heptacarboxylic acid heptamethyl ester (**1**) as the product of a cascade reaction. This compound contains several electron-deficient double bonds which enable the Michael addition of amines, and seven ester groups which implies the probability of partial amidation. There are many examples of the addition of various amines to fumaric and maleic acid esters to give biologically active compounds.[2–5] The known reaction of ammonia or primary amines with ethyl cyclohepta-1,3,5-trienecarboxylate proceeds via sequential double Michael addition of an amine molecule to the two double bonds of the heptatriene system and leads to the formation of ethyl 8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (nortrop-2-ene-2-carboxylate).[6] The ability of cycloheptatriene amino derivatives to undergo intramolecular cyclization was also used for the synthesis of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine derivatives[7–9] which exhibit anticonvulsant and neuroprotective activities. We were encouraged by the present literature to investigate the reactions of primary amines with cycloheptatriene **1**.

It was found that the reaction of cycloheptatriene **1** with the primary amines **2a–d** proceeded under mild conditions (20 °C, 24 h) leading to the formation of heterocyclic compounds **3a–d** and/or **4a–d** in overall yields greater than 90% (Scheme 1).[10] The reaction was very sensitive toward the nature of the solvent and changing the reaction conditions allowed control of the ratio of the products to a significant extent (Table 1). The nortropene derivatives **3** are formed exclusively as single stereoisomers, and the substituted 3-vinylpyridinones **4** are formed as a mixture of *E*- and *Z*-isomers, the ratios of which are determined by the amine and are only influenced weakly by the nature of the solvent (Table 1). The ^{1}H and ^{13}C NMR spectra of compounds **3** exhibit seven ester group signals and only two alkene carbon resonances at 133–135 ppm.[11] The NMR spectra of the isomeric propenylpyridinones **4** show six ester group resonances and a characteristic CH_2-group signal represented by two doublets with a geminal spin–spin coupling constant of about 17 Hz. These protons were observed in the range 3.8–4.2 ppm for the *E*-isomers, and 3.2–3.5 ppm for the *Z*-isomers.[12]

Investigating the influence of the reaction conditions on the regioselectivity revealed that less polar solvents (e.g., xylene and chloroform) increased the yield of the bicyclic compounds **3**, which is most obvious in the case of benzylamine **2a**. In contrast, polar solvents significantly increased the yields of pyridinones **4**; using methanol as the solvent gave pyridinones **4a–d** almost quantitatively with all the primary amines. Almost complete separation of the *E*- and *Z*-isomers of the benzyl derivative of pyridinone **4a** was achieved by column chromatography using silica gel. In other cases, pyridinones **4b–d** were isolated as mixtures significantly enriched with either the *E*- or *Z*-isomer. In the ^{1}H NMR spectra of these compounds, the protons of the CH_2-group are not equivalent.

* Corresponding author. Tel./fax: +7 499 135 6390.
E-mail address: tom@ioc.ac.ru (Y.V. Tomilov).

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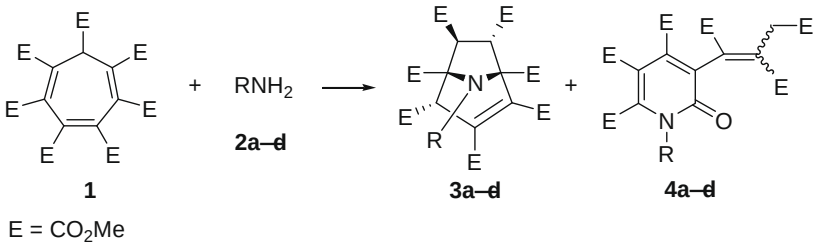


Scheme 1. Conditions: **1**:**2** = 1:1.5, 20 °C, 20–24 h, solvent (see Table 1).

Table 1
Yields of compounds **3** and **4** on varying the solvent

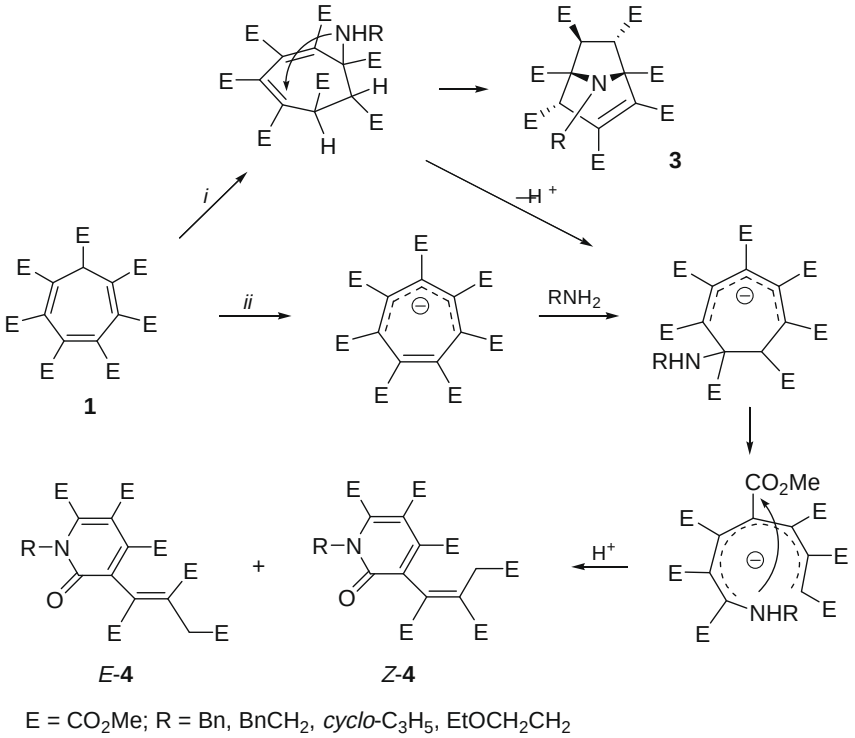
Amine	R	Solvent	Yield **3**[a] (%)	Yield **4**[a] (%)	*E*/*Z* ratio
2a	Bn	$CHCl_3$	95	—[b]	
		CH_3OH	—[b]	96	2.7:1
2b	$BnCH_2$	*p*-xylene	50	45	2.2:1
		CH_3OH	—[b]	91	2.4:1
2c	*c*-C_3H_5	*p*-xylene	73	21	1.4:1
		$CHCl_3$	47	46	1.6:1
		THF	17	77	1.4:1
		CH_3OH	—[b]	96	1.7:1
2d	$EtO(CH_2)_2$	*p*-xylene	45	46	1.9:1
		CH_3OH	—[b]	93	1:9:1

[a] Yields are for isolated (chromatographed or crystallized) materials (>96% purity by ^{1}H NMR).
[b] This compound was not observed by ^{1}H NMR.

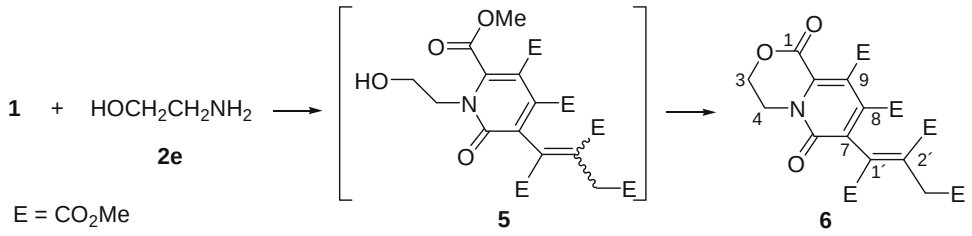
The splitting of the geminal protons can be explained by the pyridinone ring and the exocyclic double bond being orthogonal to each other with hindered rotation about the aryl-vinyl single bond.

The different structures of the products and strong dependency of the regioselectivity on the solvent polarity seem to be evidence for the existence of different mechanisms for the formation of compounds **3** and **4**. The tropene structure of **3** (similar to that formed in the reaction of ammonia or primary amines with ethyl cyclohepta-1,3,5-trienecarboxylate[6]) results from addition of the amine to the double bond of the cycloheptatriene such that both sp^3 carbon atoms are adjacent to each other. Further reaction involves an intramolecular Michael addition of the amine fragment to one of the remaining double bonds of the seven-membered ring (Scheme 2). Here the regio- and stereoselectivity are due to the most favorable spatial orientation of the ester groups during the formation of the unsaturated bicyclic framework. We have observed similar stereoselectivities in the formation of a bicyclo[3.2.0]hept-2-ene on reduction of the cycloheptatriene **1** with sodium borohydride.[13]

In polar solvents, specifically in methanol, the starting triene **1** appears to undergo initial deprotonation by the amine, which is in agreement with its proceeding transformation into the stable hepta(methoxycarbonyl)cycloheptatrienyl anion,[1] and further reaction involves addition of the amine to the double bond not participating in the negative charge delocalization within the seven-membered ring.[14] The resulting anion, which may also be formed by deprotonation of the initially formed amine adduct, see Scheme 2, undergoes ring-opening with simultaneous formation of the pyridinone ring and the isomeric trisubstituted propenyl fragment (Scheme 2).



Scheme 2. Michael addition of amines to **1**. (i) in non-polar solvents; (ii) in polar solvents with prior ionization of **1**.



Scheme 3. Conditions: **1**:**2e** = 1:1.5, 20 °C, 20–24 h, solvent: CH_2Cl_2 or CH_3OH.

A somewhat different outcome was observed in the reaction of cycloheptatriene **1** with 2-aminoethanol. In this case, the reaction gave the corresponding 3-vinylpyridin-2-one exclusively, regardless of the solvent. However, the reaction did not stop here, and the product **5** underwent further cyclization into the lactone **6**,[15] which was easily isolated from the reaction mixture by crystallization in a yield of 77% as the *E*-isomer only (Scheme 3). The structural assignment of compound **6** was strongly supported by ^1H–^1H HMBC, and ^1H–^{13}C HMQC NMR experiments.

It should be noted that the reaction of the cycloheptatriene **1** with amines is strongly influenced by the nature of the amine used. In particular, the reaction with primary amines is only possible under the mild conditions described, while the presence of bulky substituents on the amine prevents addition to the sterically hindered double bonds of the substituted cycloheptatriene. Thus, for example, no reaction occurs between **1** and dimethylamine, aniline, or *tert*-butylamine.

The compounds obtained are of interest as building blocks for the synthesis of analogs of various natural products, in particular of the tropane derivatives used in the synthesis of natural photochrome analogs[16] and also of a number of biologically active compounds including narcotic drug antagonists.[17] Pyridin-2-ones are widely used as central fragments in the synthesis of various alkaloids.[18] Despite the great variety of synthetic methods for pyridin-2-ones, the development of new synthetic routes leading to pyridinone fragments is still important.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.114.

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10. *General method for compounds* **3** and **4**: To a stirred solution of cyclohe ptatrieneheptacarboxylate **1** (1 mmol) in solvent (7 ml) (see Table 1) amine **2** (1.5 mmol) in the same solvent (0.5 ml) was added and the reaction mixture was stirred at 20 °C for 24 h. The solvent was removed in vacuo and the residue was crystallized or purified by column chromatography on silica gel using benzene–AcOEt, 2:1 as eluent.
11. *Heptamethyl 8-benzyl-8-azabicyclo[3.2.1]oct-2-ene-1,2,3,4,5,6,7-heptacarboxylate* **3a**: Colorless crystalline solid, mp 152–153 °C; ^1H NMR (300 MHz, $CDCl_3$): 3.01, 3.62, 3.69, 3.70, 3.73, 3.78 and 3.80 (all s, 7 × 3H, 7 OCH_3); 3.68 and 3.89 (both d, J = 15.6, 2 × 1H, CH_2); 4.44 (s, 1H, H(6)); 4.45 (s, 2H, H(4) and H(7)); 7.17–7.34 (m, 5H, C_6H_5). ^{13}C NMR (75.5 MHz, $CDCl_3$): 46.38 (C(6)); 48.83 (C(7)); 48.89 (CH_2); 52.47, 52.48, 52.69, 52.75, 52.78, 52.82 and 52.89 (7 OCH_3); 56.48 (C(4)); 71.99 and 72.16 (C(1) and C(5)); 127.14 (C_p); 127.99 and 128.19 ($2C_o$ and $2C_m$); 133.69 and 133.90 (C(2) and C(3)); 137.15 (C_{ipso}); 165.90, 166.43, 167.12, 168.61, 168.88, 169.71 and 170.80 (7 COO). IR (KBr): ν 2956, 1725–1748 (COO), 1626, 1436 cm^{-1}. EI-MS, m/z: (%) 605 (M^+, 2), 546 ($M^+-CO_2CH_3$, 3), 392 (5), 336 (5), 305 (5), 248 (30), 237 (5), 121 (10), 105 (5), 91 (CH_2Ph^+, 100). Anal. Calcd for $C_{28}H_{31}NO_{14}$: C, 55.54; H, 5.12; N, 2.31. Found: C, 55.59; H, 4.96; N, 2.35.
Trans (6,7)-8-(2-Ethoxyethyl)-1,2,3,4,5,6,7-heptamethoxycarbonyl-8-azabicyclo [3.2.1]oct-2-ene **3d**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, J = 7.0 Hz, 3H, CH_3), 2.83 (m, 2H, CH_2N), 3.14 and 2.28 (both ddd, ^2J = 9.8 Hz, ^3J = 6.7 and 7.2 Hz, 2 × 1H, CH_2O), 3.38 (m, 2H, OCH_2), 3.66, 3.70, 3.74, 3.75 and 3.81 (all s, 3 + 3 + 9 + 3 + 3H, 7OCH_3), 4.28 (d, J = 9.2 Hz, 1H, H(6)), 4.40 (d, J = 9.2 Hz, 1H, H(7)), 4.45 (s, 1H, H(4)); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.11 (CH_3), 44.77 (CH_2N), 46.19 (C(4)), 48.68 (C(6)), 52.40, 52.58, 52.64, 52.74, 52.79, 52.83 and 53.16 (7OCH_3), 56.48 (C(7)), 66.53 and 69.15 (CH_2OCH_2), 71.91 (C(5)), 73.05 (C(1)), 133.85 (C(3)), 134.61 (C(2)), 165.73, 166.58, 167.87, 168.54, 168.64, 169.65 and 170.67 (7COO). IR ν_{max} (NaCl) 1728–1742 (COO), 1636, 1437 cm^{-1}; EI-MS, m/z: 528 ($M^+-CO_2CH_3$, 14), 318 (8), 113 (12), 73 (28), 59 (97), 45 (100). Anal. Calcd for $C_{25}H_{33}NO_{15}$: C, 51.11; H, 5.66; N, 2.38. Found: C, 50.91; H, 5.52; N, 2.19.
12. *1-Benzyl-(3-[(1,2,3-trimethoxycarbonyl)prop-1-enyl]-4,5,6-trimethoxycarbonylpyridi n-2-one* (**4a**): Colorless oil; IR (KBr): ν 3020, 2956, 1728–1747 (COO), 1664 (C=O), 1436. EI-MS, m/z: 573 (M^+, 2), 514 ($M^+-CO_2CH_3$, 4), 392 (6), 121 (12), 105 (3), 91 (CH_2Ph^+, 100). Anal. Calcd for $C_{27}H_{27}NO_{13}$ C, 56.54; H, 4.71; N, 2.44. Found: C, 56.74; H, 4.77; N, 2.41. *E*-isomer ^1H NMR (300 MHz, $CDCl_3$): 3.61, 3.70, 3.72, 3.74, 3.76 and 3.81 (all s, 6 × 3H, 6OCH_3), 3.80 and 4.15 (both d, J = 17.0, 2 × 1H, CH_2), 5.24 and 5.35 (both d, J = 15.1, 2 × 1H, CH_2Ph), 7.18–7.37 (m, 5H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): 35.64 (CH_2), 49.70 (CH_2Ph), 52.19, 52.78, 52.89, 52.90, 52.95 and 53.40 (6OCH_3), 106.19 (C(5)), 127.35 ($2C_o$), 127.98 (C_p), 128.61 ($2C_m$), 128.89 (C(3)), 133.85 (=C(1)), 135.01 (C_i), 139.06 (=C(2)), 139.55 (C(4)), 144.82 (C(6)), 159.84 (C(2)), 162.39, 163.26, 164.95, 165.11 and 166.10 (5COO), 169.85 (CH_2COO); *Z*-isomer: ^1H NMR (300 MHz, $CDCl_3$): 3.24 and 3.39 (both d, J = 17.0, 2 × 1H, CH_2), 3.64, 3.72, 3.74, 3.77, 3.82 and 3.83 (all s, 6 × 3H, 6OCH_3), 5.23 and 5.32 (both d, J = 15.0, 2 × 1H, CH_2Ph), 7.14–7.36 (m, 5H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): 37.78 (CH_2), 49.87 (CH_2Ph), 52.26, 52.72, 52.85, 53.08, 53.23 and 53.53 (6OCH_3), 106.11 (C(5)), 124.49 (C(3)), 127.53 ($2C_o$), 128.20 (C_p), 128.69 ($2C_m$), 130.64 (C(1′)), 134.63 (C_i), 139.76 (C(2′)), 142.51 and 145.93 (C(4) and C(6)), 159.26 (C(2)), 162.01, 162.95, 164.65, 165.00 and 167.53 (5COO), 168.82 (CH_2COO).
1-(2-Ethoxyethyl)-(3-[(1,2,3-trimethoxycarbonyl)prop-1-enyl]-4,5,6-trimethoxycar bonylpy ridin-2-one (**4d**): Colorless oil; IR ν_{max} (NaCl) 1724–1744 (COO), 1668 (C=O), 1597 (C=C) cm^{-1}; EI-MS: 555 (M^+, 2), 524 (M^+-OCH_3, 4), 496 ($M^+-CO_2CH_3$, 24), 392 (20), 360 (17), 73 (94), 59 (95), 45 (100). Anal. Calcd for $C_{24}H_{29}NO_{14}$: C, 51.89; H, 5.26; N, 2.52. Found: C, 51.64; H, 5.08; N, 2.38. *E*-isomer ^1H NMR (600 MHz, $CDCl_3$): δ 1.15 (t, J = 7.0 Hz, 3H, CH_3), 3.46 (q, J = 7.0, 2H, CH_2O), 3.62 (m, 2H, OCH_2), 3.63, 3.70, 3.77, 3.79, 3.81 and 3.95 (all s, 6 × 3H, 6OCH_3), 3.81 and 4.10 (both d, ^2J = 17.0 Hz, 2 × 1H, CH_2), 4.17 and 4.26 (both br.dt, ^2J = 13.6 Hz, ^3J = 6.7 Hz, 2 × 1H, CH_2N); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.92 (CH_3), 35.59 (CH_2), 47.01 (CH_2N), 52.06, 52.61, 52.76, 52.81, 53.06, and 53.53 (6OCH_3), 66.64 and 66.87 (CH_2OCH_2), 106.64 (C(5)), 128.49 (C(3)), 133.86 (=C(1)), 138.97 (=C(2)), 139.15 (C(4)), 145.90 (C(6)), 159.58 (C(2)), 162.31, 163.56, 164.90, 165.02 and 166.02 (5COO), 169.76 (CH_2COO); *Z*-isomer ^1H NMR (600 MHz, $CDCl_3$): δ 1.14 (t, J = 7.0 Hz, 3H, CH_3), 3.23 and 3.33 (both d, ^2J = 17.0 Hz, 2 × 1H, CH_2), 3.44 (q, J = 7.0, 2H, CH_2O), 3.64 (m, 2H, OCH_2), 3.66, 3.70, 3.71, 3.78, 3.81 and 3.95 (all s, 6 × 3H, 6OCH_3), 4.21 (m, 2H, CH_2N); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.88 (CH_3), 37.57 (CH_2), 47.23 (CH_2N), 52.14, 52.57, 52.70, 52.76, 52.95, and 53.65 (6OCH_3), 66.63 and 66.83 (CH_2OCH_2), 106.55 (C(5)), 124.09 (C(3)), 130.89 (=C(1)), 139.22 (=C(2)), 142.42 (C(4)), 144.75 (C(6)), 158.96 (C(2)), 161.97, 163.32, 164.80, 164.97 and

167.40 (5COO), 168.79 (CH_2COO). The structural assignment was strongly supported by ^1H–^1H HMBC and ^1H–^{13}C HMQC NMR experiments.
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14. See the X-ray data for hepta(methoxycarbonyl)cycloheptatrienyl potassium in Ref. 1.
15. *Dimethyl 1,6-dioxo-7-[1,2,3-tris(methoxycarbonyl)propen-1-yl]-1,3,4,6-tetrahydropyrido[2,1-c][1,4]oxazine-8,9-dicarboxylate* **6**: colorless crystals, mp 203–205 °C (EtOAc). ^1H NMR (300 MHz, $CDCl_3$): 3.64, 3.72, 3.73, 3.80 and 3.87 (all s, 5 × 3H, OCH_3), 3.88 and 4.18 (both d, 2 × 1H, CH_2, ^2J = 16.9), 4.11 and 4.47 (both dt, 2 × 1H, NCH_2, ^2J = 15.4, ^3J = 6.1 and 4.2), 4.67 (dd, 2 H, OCH_2, ^3J = 6.1 and 4.2); ^{13}C NMR (75.5 MHz, $CDCl_3$): 35.39 (CH_2), 40.41 (NCH_2), 52.25, 52.94, 53.02, 53.34 and 53.57 (5 OCH_3), 65.48 (OCH_2), 118.17 (C(9)), 130.42 (=C(1́)), 134.71 and 135.32 (C(7) and C(8)), 136.88 (=C(2́)), 138.10 (C(10)), 157.10 and 158.00 (C(1) and C(6)), 163.98, 164.69, 165.33, 165.88, 169.94 (5COO). IR (KBr): *ν* 3012, 2956, 1720–1742, 1656, 1440. EI-MS, *m*/*z*: 495 (M^+, 3), 464 (3), 436 (48), 59 (100). Anal. Calcd for $C_{21}H_{21}NO_{13}$ C, 50.92; H, 4.27; N, 2.83. Found: C, 50.79; H, 4.22; N, 2.71.
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