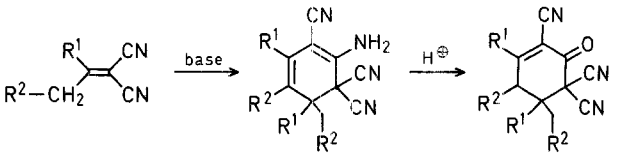
Syntheses with Unsaturated Nitriles; II. Selective Monoesterification of 2,6,6-Tricyano-2-cyclohexenones by Transannular Rearrangement

Maciej ADAMCZYK, Julian MIREK, Maria MOKROSZ

Department of Organic Chemistry, Jagiellonian University, PL-30-060 Kraków, Poland

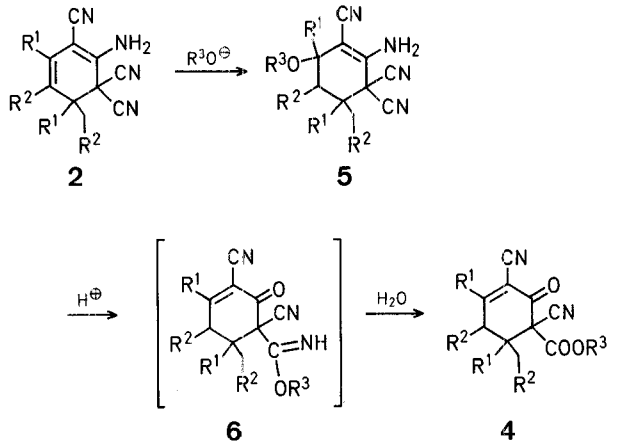
Recently, we examined the dimerization reaction of alkylidenemalononitriles **1** and developed a convenient synthesis of 2,6,6-tricyano-2-cyclohexenones **3** (3-oxo-2,6,6-tricyanocyclohexenes) and pointed at the possibility of alcoholysis of the tricyanocyclohexenone derivatives to monoesters[1].



1 **2** **3**

Now we report on a selective method of synthesis of 1,3-dicyano-2-oxo-4,6,6-trialkyl-3-cyclohexene-1-carboxylates **4**.

The most common method for preparation of esters from nitriles is the alcoholysis in the presence of acid[2]. This procedure, when applied to 2,6,6-tricyano-2-cyclohexenones **3**, leads to a mixture of mono-, di- and triesters which is hardly separable. Based on the fact[1,3] that the methoxy adduct of 1-amino-2,6,6-tricyano-3,5,5-trimethyl-cyclohexene in aqueous-ethanolic hydrochloric acid solution undergoes transformation to methyl 1,3-dicyano-2-oxo-4,6,6-trimethyl-3-cyclohexene-1-carboxylate we were able to elaborate an efficient method leading to monoketoesters **4**.



2 **5** **6** **4**

We have prepared the methoxy and ethoxy adducts **5** by treating some ylidenemalononitrile dimers **2** with a base in an appropriate alcohol. The formation of methoxy adducts occurs smoothly with about 80% yield in the presence of a catalytic amount of sodium methoxide. On the other hand, the synthesis of ethoxy adducts generally requires the use of sodium hydroxide and the yield is lower in comparison to the methoxy adducts. Moreover, alkoxy adducts can be easily obtained in one step from ylidenemalononitriles as described previously[1] (Table 1).

The transformation of adducts **5** to monoketoesters **4** occurs via a transannular rearrangement which involves migration of the alkoxy group to the protonated cyano group at C-6. The imidic ester **6** is formed as an intermediate which undergoes further hydrolysis to the monoketoester **4**. Our attempts on the rearrangement of the adducts according to the procedure described for 1-amino-3-methoxy-2,6,6-tricyano-3,5,5-trimethylcyclohexene failed. We found that the best conditions for this reaction are refluxing of the adducts **5** in dilute hydrochloric acid (18%). However, in the case of rearrangement of adducts **5i** and **5j** we have isolated the corresponding amide **7** as a product of hydrolysis of the intermediate imidic ester **6** by another route with the ester as a by-product (10%). We have determined that, in such cases, the addition of a 2:1 mixture of a suitable alco-

0039-7881/80/1132-0916 $ 03.00

Table 1. 1-Amino-3-ethoxy(or -methoxy)-2,6,6-tricyanocyclohexenes **5**

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	^{1}H-N.M.R. δ [ppm]	M.S. *m/e* (M^+)
5a	H_3C	H	H_3C	79–80	210–212°	$C_{13}H_{16}N_4O$ (244.3)	1.1 (d, 6H, CH_3); 1.42 (d, 2H, CH_2); 1.8 (s, 3H, $H_3C-C=$); 3.7 (s, 3H, OCH_3); 7.97 (s, 2H, NH_2)	244
5b	H_3C	H	C_2H_5	42–58	151–152°	$C_{14}H_{18}N_4O$ (258.3)	1.8 (m, 6H, CH_3 + CH_3CH_2O); 4.15 (q, J = 10 Hz, 2H, CH_3CH_2O); 7.92 (s, 2H, NH_2)	258
5c	C_2H_5	H	H_3C	98	103–105°	$C_{15}H_{20}N_4O$ (272.3)	0.7–2.1 (m, 15H); 3.75 (s, 3H, OCH_3); 5.17 (s, 2H, NH_2)	272
5d	C_2H_5	H	C_2H_5	69	146–147°	$C_{16}H_{22}N_4O$ (286.4)	0.8–2.1 (m, 18H); 4.17 (q, J = 10 Hz, 2H, CH_3CH_2O); 5.12 (s, 2H, NH_2)	286
5e	n-C_3H_7	H	H_3C	84	116–117°	$C_{17}H_{24}N_4O$ (300.4)	0.8–2.1 (m, 19H); 3.8 (s, 3H, OCH_3); 5.2 (s, 2H, NH_2)	300
5f	n-C_3H_7	H	C_2H_5	84	142–143°	$C_{18}H_{26}N_4O$ (314.4)	0.8–2.1 (m, 22H); 4.2 (q, J = 8.75 Hz, 2H, CH_3CH_2O); 5.15 (s, 2H, NH_2)	314
5g	$-(CH_2)_3-$		H_3C	80	210°	$C_{17}H_{20}N_4O$ (296.4)	1.3–2.5 (m, 15H); 3.75 (s, 3H, OCH_3); 5.5 (s, 2H, NH_2)	296
5h	$-(CH_2)_3-$		C_2H_5	72	173–174°	$C_{18}H_{22}N_4O$ (310.4)	1.2–2.5 (m, 18H); 4.25 (q, J = 8.75 Hz, 2H, CH_3CH_2O); 5.05 (s, 2H, NH_2)	310
5i	$-(CH_2)_4-$		H_3C	79	220–222°	$C_{19}H_{24}N_4O$ (324.4)	1.3–2.3 (m, 19H); 3.82 (s, 3H, OCH_3); 4.8 (s, 2H, NH_2)	324
5j	$-(CH_2)_4-$		C_2H_5	70	202–206°	$C_{20}H_{26}N_4O$ (338.4)	1.3–2.4 (m, 22H); 4.22 (q, J = 8.75 Hz, 2H, CH_3CH_2O)	338

[a] Yield of isolated product.
[b] The microanalyses were in good agreement with the calculated values: C, ±0.28; H, ±0.22; N, ±0.19.

Table 2. Ethyl (or Methyl) 1,3-Dicyano-2-oxo-3-cyclohexene-1-carboxylates **4**

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. ν [cm^{-1}]	^{1}H-N.M.R. δ [ppm]	M.S. *m/e* (M^+)
4a	H_3C	H	H_3C	90–95	140°, 142–143°	$C_{13}H_{14}N_2O_3$ (246.3)	2260 (CN); 1750, 1700 (CO)	1.2 (d, 6H, CH_3); 2.35 (s, 3H, $H_3C-C=$); 2.75 (d, 2H, CH_2); 3.8 (s, 3H, OCH_3)	246
4b	H_3C	H	C_2H_5	92–93	109° 108–109°	$C_{14}H_{16}N_2O_3$ (260.3)	2260 (CN); 1740, 1690 (CO)	1.2–1.45 (m, 9H); 2.4 (s, 3H, $H_3C-C=$); 2.75 (d, 2H, CH_2); 4.42 (q, J = 7.5 Hz, 2H, CH_3CH_2O)	260
4c	C_2H_5	H	CH_3	95	75–77°	$C_{15}H_{18}N_2O_3$ (274.3)	2260 (CN); 1760, 1710 (CO)	0.7–1.4 (m, 11H); 2.67 (q, J = 10 Hz, 4H, $CH_2-C=$); 3.85 (s, 3H, OCH_3)	274
4d	C_2H_5	H	C_2H_5	72	69–70°	$C_{16}H_{20}N_2O_3$ (288.3)	2260 (CN); 1750, 1700 (CO)	0.9–1.4 (m, 16H); 2.65 (q, J = 8.75 Hz, 2H, $CH_2-C=$); 4.27 (q, J = 8.75 Hz, 2H, CH_3CH_2O)	288
4e	n-C_3H_7	H	CH_3	91	oil	$C_{17}H_{22}N_2O_3$ (302.4)	2260 (CN); 1760, 1700 (CO)	0.8–1.9 (m, 15H); 2.5–3.0 (m, 4H, $CH_2-C=$); 3.87 (s, 3H, OCH_3)	302
4f	n-C_3H_7	H	C_2H_5	88	97–100°	$C_{18}H_{24}N_2O_3$ (316.4)	2260 (CN); 1750, 1705 (CO)	0.8–1.85 (m, 18H); 2.5–2.9 (m, 4H, $CH_2-C=$); 4.30 (q, J = 8.75 Hz, 2H, CH_3CH_2O)	316
4g	$-(CH_2)_3-$		CH_3	83	130–131°	$C_{17}H_{16}N_2O_3$ (298.3)	2260 (CN); 1750, 1700 (CO)	1.5–2.4 + 2.7–3.3 (2 m, 15H); 3.9 (s, 3H, OCH_3)	298
4h	$-(CH_2)_3-$		C_2H_5	81	125–128°	$C_{18}H_{20}N_2O_3$ (312.4)	2255 (CN); 1750, 1710 (CO)	1.1–3.2 (m, 18H); 4.3 (q, J = 8.75 Hz, 2H, CH_3CH_2O)	312
4i	$-(CH_2)_4-$		CH_3	49	134°	$C_{19}H_{22}N_2O_3$ (326.4)	2260 (CN); 1760, 1710 (CO)	1.0–2.25 (m, 19H); 3.82 (s, 3H, OCH_3)	326
4j	$-(CH_2)_4-$		C_2H_5	47	190–191°	$C_{20}H_{24}N_2O_3$ (340.4)	2260 (CN); 1740, 1710 (CO)	1.1–3.3 (m, 22H); 4.27 (q, J = 8.75 Hz, 2H, CH_3CH_2O)	340
7	$-(CH_2)_4-$		$R^3O=$ NH_2	40	222–225°	$C_{18}H_{21}N_3O_2$ (311.4)	3340 (NH); 2290 (CN); 1770, 1725 (CO)	1.2–2.4 (m, 16H); 2.97 (s, 3H, OCH_3); 4.65 (s, 2H, NH_2)	311

[a] Yield of isolated product.
[b] The microanalyses were in good agreement with the calculated values: C, ±0.23; H, ±0.15; N, ±0.12.

hol with concentrated hydrochloric acid favours the formation of monoketoesters as the main product in satisfactory yield (Table 2).

1-Amino-3-methoxy-2,6,6-tricyanocyclohexenes 5 (R^3 = CH_3); General Procedure:

The dimer **2** (4 mmol), methanol (10 ml), and a few drops of methanolic sodium methoxide are heated to dissolve the dimer. Then

the mixture is stirred for 2 h. The separated crystals of adduct are isolated and the rest of adduct is precipitated by adding a small amount of water to the mother liquid; yield: ~80%. Analytical samples are crystallised from methanol or ethanol.

1-Amino-3-ethoxy-2,6,6-tricyanocyclohexenes 5 ($R^3 = C_2H_5$); General Procedure:
The dimer **2** (4 mmol), ethanol (10 ml), and sodium hydroxide (0.1 g) are treated as in the procedure described above; yield: ~70%.

Methyl 1,3-Dicyano-2-oxo-3-cyclohexene-1-carboxylates 4 ($R^3 = CH_3$); General Procedure:
The adduct **5** ($R^3 = CH_3$; 4 mmol) in 18% hydrochloric acid (10 ml) is heated under reflux for 1 h. The mixture is then allowed to cool and a few drops of methanol are added to solidify the oily product. The solidified product is crystallised from methanol.

Ethyl 1,3-Dicyano-2-oxo-cyclohexene-1-carboxylate 4 ($R^3 = C_2H_5$):
The adduct **5** ($R^3 = C_2H_5$; 2 mmol) in 18% hydrochloric acid (10 ml) is worked up as in the procedure described above.

2′,4′-Dicyano-2′-methoxycarbonyl-3′-oxo-3′,4′,4′a,5′,6′,7′,8′,8′a-octahydro-spiro[cyclohexane-1,1′(2′*H*)-naphthalene] (4i):
The adduct **5i** (3 mmol) is refluxed for 1 h in a mixture of methanol (20 ml) and concentrated hydrochloric acid (10 ml). The mixture is then allowed to cool and precipitated 2′-aminocarbonyl derivative is filtered off. The ester **4i** is precipitated from the mother liquid by adding water (10 ml) and crystallised from methanol.

2′,4′-Dicyano-2′-ethoxycarbonyl-3′-oxo-3′,4′,4a′,5′,6′,7′,8′,8′a-octahydro-spiro[cyclohexane-1,1′(2′*H*)-naphthalene] (4j):
The adduct **5j** (2 mmol) is refluxed for 1 h in a mixture of methanol (20 ml) and concentrated hydrochloric acid (10 ml). The mixture is then allowed to cool and precipitated ester **4j** is filtered off. The 2′-aminocarbonyl derivative is precipitated from the mother liquid by adding water (10 ml).

Received: July 18, 1980

[1] J. Mirek, M. Adamczyk, M. Mokrosz, *Synthesis* **1980**, 296.
[2] W. Schneider, F. Schumann, G. Modjesch, *Pharmazie* **25**, 724 (1970).
E. H. Zilberman, *Reactions of Nitriles*, chapter 6, Moscow, 1972.
[3] J. K. Williams, *J. Org. Chem.* **28**, 1054 (1963).

0039-7881/80/1132-0918 $ 03.00