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An Efficient Synthesis of Trialkyl *N*-Alkyl-6-methyl-2-pyridone-3,4,5-tricarboxylates

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Summary. An efficient synthesis of trialkyl *N*-alkyl-6-methyl-2-pyridone-3,4,5-tricarboxylates from three-component reaction of the zwitterions generated from dialkyl acetylenedicarboxylates and alkyl isocyanides with alkyl 2-chloroacetoacetates is described.

Keywords. *N*-Alkyl-2-pyridone; Alkyl isocyanide; Acetylenic ester; 2-Chloroacetoacetates.

Introduction

N-Alkyl-2-pyridones are important intermediates in the synthesis of polycyclic compounds of biological significance as illustrated by the recent synthesis of camptothecin family of anti-tumor agents [1]. 2-Pyridones are structural sub-units of naturally occurring compounds, such as the heterocyclic annelated *N*-alkyl-2-pyridones, which have emerged as antifungal [2, 3], anti-bacterial [4], anti-viral [5], and anti-thrombotic [6] agents. However, there is still a need for methods allowing the efficient synthesis of *N*-alkyl-2-pyridones.

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 [7–10]. MCRs have been used to create diversity-oriented and biased combinatorial assemblies, and for the synthesis of highly complex natural products. As part of our current studies on the development of new routes in heterocyclic synthesis [11–17], we report an efficient one-pot synthesis of trialkyl *N*-alkyl-6-methyl-2-pyridone-3,4,5-tricarboxylates **1**.

Results and Discussion

The reaction of the alkyl isocyanides **2** with dialkyl acetylenedicarboxylates **3**, in presence of alkyl 2-chloroacetoacetates **4** in CH_2Cl_2 proceeded smoothly at ambient temperature. After 3 h, the reaction mixture was saturated with a few drops of water and was stirred overnight to afford the target compounds **1** in 78–90% yields (based on the isocyanide; Scheme 1). The structures of compounds **1a**–**1i** were deduced from their elemental analyses and their IR, ^{1}H, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values.

Compound **1a** was characterized on the basis of its spectroscopic data. While the IR spectrum showed strong absorptions due to the ester carbonyl groups at 1727–1714 cm^{-1}, the carbonyl absorption of the 2-pyridone system was observed at 1650 cm^{-1}. The ^{1}H NMR spectrum exhibited the three carbomethoxy groups as singlets at $\delta = 3.81$, 3.83, and 3.86 ppm. The methyl and *tert*-butyl protons displayed singlets

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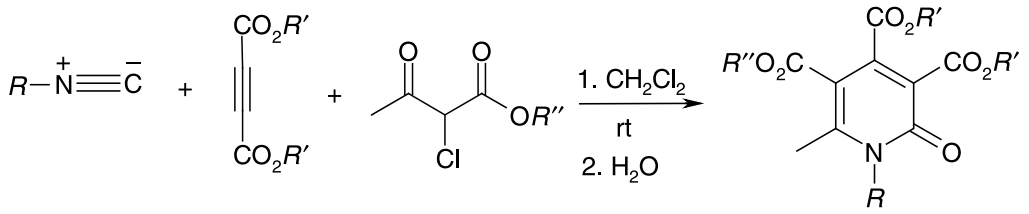


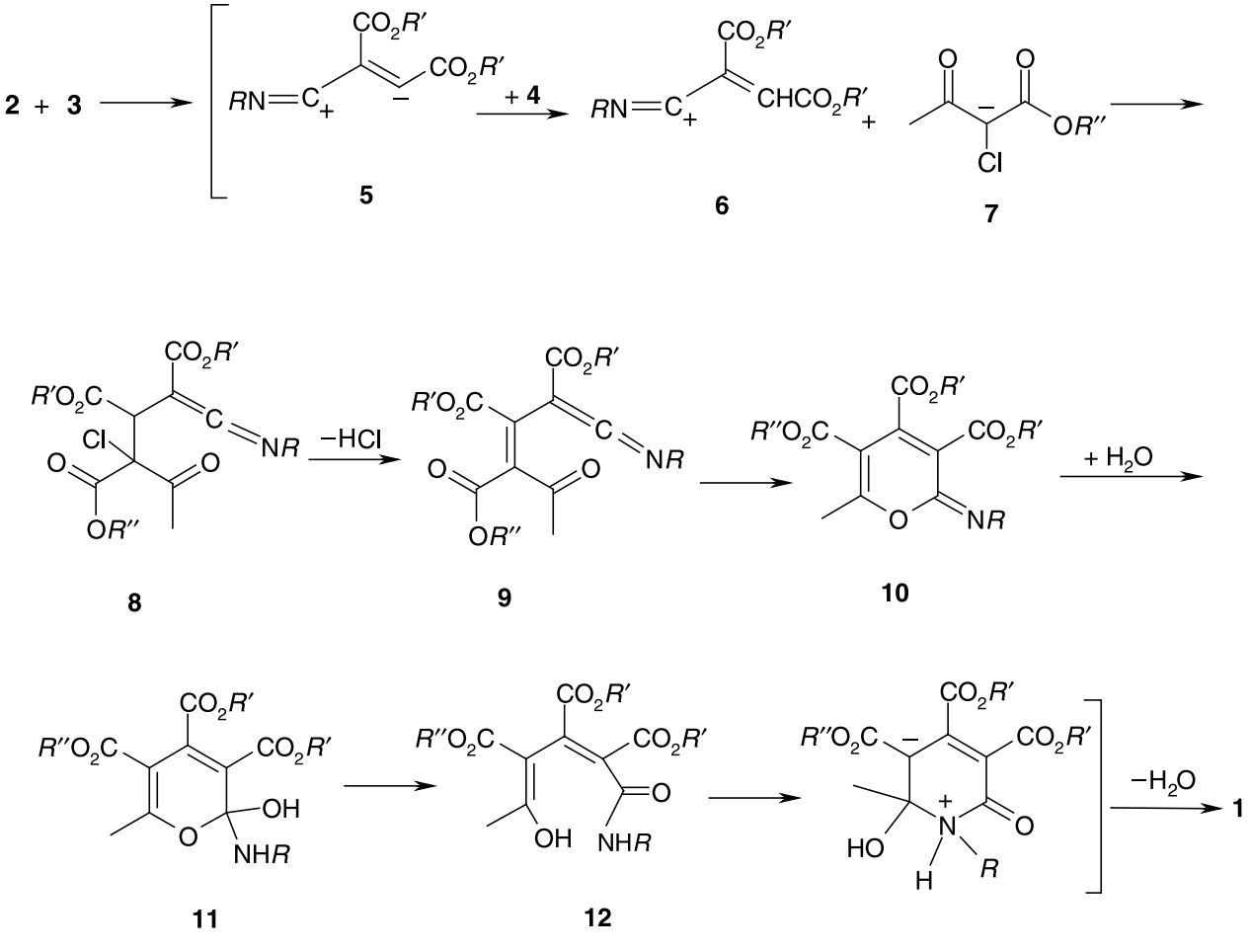
2	R
a	^{t}Bu
b	Cyclohexyl

3	R′
a	Me
b	Et
c	^{i}Pr
d	^{t}Bu

4	R″
a	Me
b	Et

1	R	R′	R″
a	^{t}Bu	Me	Me
b	^{t}Bu	Et	Me
c	^{t}Bu	^{i}Pr	Me
d	^{t}Bu	^{t}Bu	Me
e	Cyclohexyl	Me	Me
f	Cyclohexyl	Et	Me
g	Cyclohexyl	^{t}Bu	Me
h	^{t}Bu	Me	Et
i	^{t}Bu	^{t}Bu	Et

Scheme 1



Scheme 2

at $\delta = 2.12$ and 1.44 ppm. In the ^{13}C NMR spectrum, the peak at $\delta = 172.6$ ppm was assigned to the 2-pyridone carbonyl functionality. The ester groups were visible at $\delta = 163.5$, 163.6, and 167.4 ppm. The methoxy carbons were observed at $\delta = 53.0$, 53.5, and 53.8 ppm. The signal at $\delta = 68.4$ ppm was attributed to the quaternary carbon atom of the *tert*-butyl group. The ^1H and ^{13}C NMR spectra of **1b**–**1e** are similar to those of **1a** except for the alkyl residues, which exhibited characteristic signals with appropriate chemical shifts. Structure **1** was distinguished from intermediate **10** (see Scheme 2) on the basis of the observation of only four signals above $\delta = 140$ ppm in the ^{13}C spectrum. Five signals above $\delta = 140$ ppm are expected for **10**.

The following mechanism may be invoked for the formation of compound **1**. Conceivably the starting point of the reaction is the formation of a 1:1 zwitterionic species [18] **5** between the isocyanide and the acetylenic ester, which is protonated by the CH-acidic **4**. Then, the positively charged ion might be attacked by the enolate anion of **4** to produce the ketenimine **8**. Elimination of HCl from **8** leads to **9**, which undergoes electrocyclic reaction [18] to form the pyrane derivative **10**. Isomerisation of **10** to **1** takes place in the presence of moisture.

In conclusion, we report a novel transformation involving alkyl isocyanides and activated acetylenes in the presence of alkyl 2-chloroacetoacetates, which affords trialkyl *N*-alkyl-6-methyl-2-pyridone-3,4,5-tricarboxylates. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of functionalized 2-pyridones.

Experimental

Compounds **2**–**4** were obtained from Fluka and were used without further purification. Mp: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values.

*General Procedure for the Preparation of Compounds **1***

To a stirred solution of 2 mmol **3** and 2 mmol **4** in 10 cm^3 CH_2Cl_2 was added dropwise a mixture of 2 mmol **2** in 3 cm^3 CH_2Cl_2 at 0°C over 5 min. The reaction was allowed to warm to room temperature and stirred for 3 h. Then, 0.5 cm^3 H_2O were added and it was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; *n*-hexane/*AcOEt* 4/1) to afford the pure adducts.

Trimethyl N-tert-butyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1a**, $C_{16}H_{21}NO_7$)

Yellow oil, yield 0.51 g (76%); IR (KBr): $\bar{\nu} = 1727$, 1714, 1650, 1613 (4C=O) cm^{-1}; ^1H NMR: $\delta = 1.44$ (9H, s, C*Me*$_3$), 2.12 (3H, s, Me), 3.81, 3.83, 3.86 (9H, 3s, 3MeO) ppm; ^{13}C NMR: $\delta = 25.6$ (Me), 28.8 (C*Me*$_3$), 53.0, 53.5, 53.8 (3MeO), 61.4 (C–N), 130.0, 134.0, 137.0, 138.0 (4C), 163.5, 163.6, 167.4, 172.6 (4C=O) ppm; EI-MS: m/z (%) = 339 (M^+, 8), 324 (18), 308 (78), 282 (46), 280 (84), 221 (82), 57 (100).

3,4-Diethyl 5-methyl N-tert-butyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1b**, $C_{18}H_{25}NO_7$)

Yellow oil, yield 0.56 g (77%); IR (KBr): $\bar{\nu} = 1727$, 1714, 1650, 1615 (4C=O) cm^{-1}; ^1H NMR: $\delta = 1.31$ (3H, t, $^3J = 7.1$ Hz, Me), 1.33 (3H, t, $^3J = 7.1$ Hz, Me), 1.44 (9H, s, C*Me*$_3$), 2.12 (3H, s, Me), 3.86 (3H, s, MeO), 4.26 (2H, q, $^3J = 7.1$ Hz, CH_2O), 4.28 (2H, q, $^3J = 7.1$ Hz, CH_2O) ppm; ^{13}C NMR: $\delta = 14.4$, 14.5, 25.8 (3Me), 28.8 (C*Me*$_3$), 53.8 (MeO), 61.4 (C–N), 62.2, 63.0 ($2CH_2O$), 129.9, 134.0, 138.0, 138.7 (4C), 163.5, 164.0, 165.2, 172.7 (4C=O) ppm; EI-MS: m/z (%) = 367 (M^+, 5), 310 (34), 308 (65), 251 (41), 177 (44), 73 (62), 57 (100).

3,4-Diisopropyl 5-methyl N-tert-butyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1c**, $C_{20}H_{29}NO_7$)

Yellow oil, yield 0.59 g (75%); IR (KBr): $\bar{\nu} = 1725$, 1714, 1650, 1615 (4C=O) cm^{-1}; ^1H NMR: $\delta = 1.23$ (6H, d, $^3J = 6.2$ Hz, CH*Me*$_2$), 1.25 (6H, d, $^3J = 6.2$ Hz, CH*Me*$_2$), 1.49 (9H, s, C*Me*$_3$), 2.11 (3H, s, Me), 3.74 (3H, s, MeO), 5.00 (1H, hept, $^3J = 6.2$ Hz, C*H*Me$_2$), 5.10 (1H, hept, $^3J = 6.2$ Hz, C*H*Me$_2$) ppm; ^{13}C NMR: $\delta = 22.0$, 22.1, 26.0, 26.6 (4 Me), 28.9 (C*Me*$_3$), 53.7 (MeO), 61.3 (C–N), 69.9, 71.2 (2CHO), 129.6, 134.5, 138.3, 138.9 (4C), 163.5, 163.6, 164.7, 172.6 (4C=O) ppm; EI-MS: m/z (%) = 395 (M^+, 7), 364 (31), 326 (63), 207 (37), 210 (44), 161 (82), 87 (29), 57 (100).

3,4-Di-tert-butyl 5-methyl N-tert-butyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1d**, $C_{22}H_{33}NO_7$)

Yellow oil, yield 0.67 g (80%); IR (KBr): $\bar{\nu} = 1725$, 1714, 1650, 1615 (4C=O) cm^{-1}; ^1H NMR: $\delta = 1.42$, 1.45, 1.50 (27H, 3s, 3C*Me*$_3$), 2.13 (3H, s, Me), 3.77 (3H, s, MeO) ppm; ^{13}C NMR: $\delta = 26.0$ (Me), 28.4, 28.9, 29.0 (3C*Me*$_3$), 53.5 (MeO), 61.3 (C–N), 82.8, 83.1 (2C–O), 129.9, 134.0, 138.0, 138.7 (4C), 162.7, 163.2, 163.4, 168.0 (4C=O) ppm; EI-MS: m/z (%) = 423 (M^+, 6), 366 (33), 309 (40), 208 (46), 151 (62), 57 (100).

3,4-Trimethyl N-cyclohexyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1e**, $C_{18}H_{23}NO_7$)

Orange oil, yield 0.56 g (77%); IR (KBr): $\bar{\nu} = 1730$, 1720, 1660, 1625 (4C=O) cm^{-1}; ^1H NMR: $\delta = 1.24$–1.78 (10H, m, $5CH_2$), 1.60 (3H, s, Me), 3.71 (1H, m, CHN), 3.78, 3.81,

3.87 (9H, 3s, 3MeO) ppm; ^{13}C NMR: $\delta = 24.3$, 25.5 ($2CH_2$), 25.6 (Me), 25.9, 29.3, 29.4 ($3CH_2$), 50.2 (CHN), 53.0, 53.5, 53.8 (3MeO), 130.0, 134.0, 137.1, 138.0 (4C), 163.5, 163.6, 164.7, 172.2 (4C=O) ppm; EI-MS: m/z (%) = 365 (M^+, 9), 306 (36), 264 (24), 205 (65), 148 (84), 101 (100), 59 (38).

3,4-Diethyl 5-methyl N-cyclohexyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1f**, $C_{20}H_{27}NO_7$)
Orange oil, yield 0.56 g (72%); IR (KBr): $\bar{\nu} = 1727$, 1714, 1650, 1615 (4C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.30$ (3H, t, $^3J = 7.1$ Hz, Me), 1.32 (3H, t, $^3J = 7.1$ Hz, Me), 1.24–1.78 (10H, m, $5CH_2$), 1.58 (3H, s, Me), 3.71 (1H, m, CH–N), 3.87 (3H, s, MeO), 4.27 (2H, q, $^3J = 7.1$ Hz, CH_2O), 4.30 (2H, q, $^3J = 7.1$ Hz, CH_2O) ppm; ^{13}C NMR: $\delta = 14.4$, 14.7 (2Me), 24.3, 25.5 ($2CH_2$), 25.8 (Me), 25.9, 29.3, 29.4 ($3CH_2$), 50.2 (N–CH), 53.0 (MeO), 62.2, 63.0 ($2CH_2O$), 129.9, 132.9, 138.0, 138.7 (4C), 163.5, 164.1, 165.3, 172.8 (4C=O) ppm; EI-MS: m/z (%) = 393 (M^+, 7), 334 (36), 233 (56), 247 (49), 174 (34), 101 (100), 73 (32), 59 (21).

3,4-Di-tert-butyl 5-methyl N-cyclohexyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1g**, $C_{22}H_{31}NO_7$)
Orange oil, yield 0.67 g (75%); IR (KBr): $\bar{\nu} = 1727$, 1716, 1655, 1615 (4C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.11$–1.76 (10H, m, $5CH_2$), 1.45 (9H, s, C*Me*$_3$), 1.50 (9H, s, C*Me*$_3$), 2.13 (3H, s, Me), 3.67 (1H, m, CH–N), 3.77 (3H, s, MeO) ppm; ^{13}C NMR: $\delta = 23.9$, 25.4, 25.6 ($3CH_2$), 25.8 (Me), 28.1, 28.2 (2C*Me*$_3$), 29.1 (CH_2), 53.8 (N–CH), 58.3 (MeO), 80.3, 83.0 (2C–O), 129.9, 134.0, 138.0, 138.7 (4C), 162.7, 163.5, 163.6, 169.3 (4C=O) ppm; EI-MS: m/z (%) = 421 (M^+, 8), 364 (38), 307 (53), 263 (32), 206 (36), 101 (82), 57 (100).

3,4-Dimethyl 5-ethyl N-cyclohexyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1h**, $C_{17}H_{23}NO_7$)
Yellow oil, yield 0.54 g (76%); IR (KBr): $\bar{\nu} = 1727$, 1715, 1650, 1620 (4C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.28$ (3H, t, $^3J = 7.1$ Hz, Me), 1.37 (9H, s, C*Me*$_3$), 2.12 (3H, s, Me), 3.62, 3.67 (6H, 2s, 2MeO), 4.20 (2H, q, $^3J = 7.1$ Hz, CH_2) ppm; ^{13}C NMR: $\delta = 28.3$, 29.5 (2Me), 30.4 (C*Me*$_3$), 50.2 (C–N), 52.2, 52.3 (2MeO), 53.2 (CH_2O), 129.1, 134.0, 138.0, 138.7 (4C), 162.7, 163.5, 163.8, 169.9 (4C=O) ppm; EI-MS: m/z (%) = 353 (M^+, 6), 322 (38), 296 (48), 229 (22), 198 (27), 139 (50), 57 (100).

3,4-Di-tert-butyl 5-ethyl N-cyclohexyl-6-methyl-2-pyridone-3,4,5-tricarboxylate (**1i**, $C_{23}H_{35}NO_7$)
Yellow oil, yield 0.69 g (79%); IR (KBr): $\bar{\nu} = 1730$, 1718, 1650, 1610 (4C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.32$ (3H, t, $^3J = 7.1$ Hz, Me), 1.42, 1.45, 1.50 (27H, 3s, 3C*Me*$_3$), 2.12 (3H, s, Me), 4.28 (2H, q, $^3J = 7.1$ Hz, CH_2) ppm; ^{13}C NMR: $\delta = 22.5$, 25.8 (2Me), 28.4, 28.9, 29.1 (3C*Me*$_3$), 53.2 (CH_2O), 61.3 (C–N), 82.1, 83.0 (2C–O), 128.9, 133.7, 138.1, 138.7 (4C), 163.0, 163.5, 163.8, 169.8 (4C=O) ppm; EI-MS: m/z (%) = 437 (M^+, 8), 380 (32), 323 (38), 321 (28), 220 (34), 163 (61), 101 (45), 57 (100).

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