Iranian Journal of Organic Chemistry Vol. 2, No. 4 (2010) 519-522

Synthesis and dynamic ^{1}H NMR study of dialkyl-2-[*N*-acetyl-*N*-(alkyl or aryl)carbamoyl]butandioate derivatives

Malek Taher Maghsoodlou[a], Nourallah Hazeri[a], Sayyed Mostafa Habibi Khorassani[*a], Ghasem Marandi[b], Majid Moradian[c], and Vahideh Soleymani [a]

[a] *Department of Chemistry, The University of Sistan and Balouchestan, P. O. Box 98135-674, Zahedan, Iran*
[b] *Department of Chemistry, Faculty of Science, Payame Noor University of Khoy, Khoy, Iran*
[c] *Department of Chemistry, Islamic Azad University, Qaemshahr Branch, Qaemshahr, Iran*

Abstract: The 1:1 adduct intermediate of alkyl or aryl isocyanides and dialkyl acetylenedicarboxylates were protonated by acetic acid to produce dialkyl-2-[*N*-acetyl-*N*-(alkyl or aryl)carbamoyl]butandioate derivatives and dynamic ^{1}H NMR effects were observed in these compounds. The calculated free-energy of activation ($\Delta G\neq$) for restricted rotation around the aryl-nitrogen single bonds in dimethyl-2-[*N*-acetyl-*N*-(2, 6-dimethyphenyl)carbamoyl]butandioate (**3d**) amounts to 58.2 ± 2 kJ.mol^{-1} with first order rate constant (k=189.3 s^{-1}) at appropriate temperature.

Keywords: Isocyanides, Acetylenic esters, Acetic acid, Dynamic NMR, Dialkyl-2-[*N*-acetyl-*N*-(alkyl or aryl)carbamoyl]butandioate derivatives, The free-energy of activation.

Introduction

The development of simple synthetic routs for widely used organic compounds from readily available reagents is one of the major tasks in organic chemistry [1]. Multicomponent reactions (MCRs) play a key role in organic chemistry due to the fact that highly complex structures can be formed in a simple one-pot process [2]. The 1:1 adduct intermediate of isocyanides and acetylenic esters has a synthetic potential because it can be trapped by many functional groups such as aldehydes, carbonyls, proton source compounds and so on [3]. We wish to report a simple synthesis of dialkyl-2-[*N*-acetyl-*N*-(alkyl or aryl)carbamoyl]butandioate derivatives by reaction between alkyl or aryl isocyanides and acetylenic esters in the presence of acetic acid.

Results and discussion

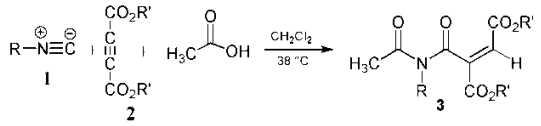
The reaction of isocyanides **1** with dialky acetylenedicarboxylates **2** in the presence of acetic acid undergo a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature, to produce dialkyl-2-[*N*-acetyl-*N*-(alkyl or aryl) carbamoyl] butandioate derivatives **3** in high yields (see Scheme **1**).

*Corresponding author. Tel/Fax: +98-541-2416586; E-Mail: *smhabibius@yahoo.com*

The structures of compounds **3a-f** were deduced from their IR, ^{1}H- and ^{13}C-NMR spectra as well as Mass spectra. The mass spectrum of **3a** displayed the molecular ion peak at appropriate *m/z* value. The IR spectrum of compound **3a** showed strong absorption peak at carbonyl region (1726 and 1697 cm^{-1}) in agreement with proposed structure.

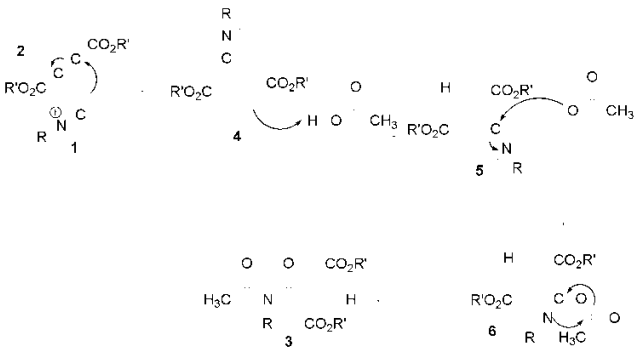
The ^{1}H NMR spectrum of compound **3a** exhibited four single sharp lines arising from acetyl (δ= 2.33 ppm), two methoxycarbonyl groups (δ= 3.69 and 3.77 ppm) and vinylic proton (δ= 6.54 ppm), respectively. Ten protons of cyclohexyl resonate at (δ= 1.91–2.19 ppm) and the methine CH resonate at (δ= 3.56 ppm) respectively. The ^{13}C NMR spectrum of compound **3a** showed thirteen distinct resonances according to the dimethyl 2-[*N*-acetyl-*N*-(cyclohexyl)carbamoyl]butandioate structure. Other assignments of these compounds are given in experimental section. The ^{1}H- and ^{13}C- NMR spectra of compounds **3b-f** are similar to those of **3a**, except for the esters and alkyl or aryl moieties, which exhibit characteristic signals with appropriate chemical shifts (see experimental section).

Although we have not established the mechanism of the reaction between the isocyanides and the acetylenic esters in the presence of acetic acid in experimental



3	R'	R	(%) Yield
a	Me	cyclohexyl	94
b	Me	benzyl	92
c	*t*-butyl	benzyl	95
d	Me	2, 6-dimethylphenyl	92
e	Et	2, 6-dimethylphenyl	93
f	*t*-butyl	2, 6-dimethylphenyl	90

Scheme 1. Reaction between isocyanides and acetylenic esters in the presence of acetic acid.

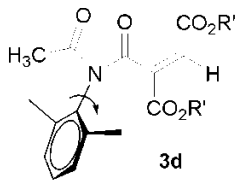


Scheme 2. Proposed mechanism for preparation of dialkyl-2-[*N*-acetyl-*N*-(alkyl or aryl)carbamoyl]butandioate derivatives.

manner, a proposed mechanism is illustrated in Scheme **2**.

On the basis of the well established chemistry of isocyanides [4-6], it is reasonable to assume that the compound **3** apparently results from initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct **4** by acetic acid, followed by attack of the acetate anion on the positively charged ion **5** to form imidoyl carboxylate **6**, which undergoes rearrangement [7-8] under the reaction condition employed, to produce the compound **3** (Scheme **2**).

We also observed dynamic NMR effects on ^{1}H NMR spectrum of compound **3d**. The ^{1}H NMR spectrum of **3d** in $CDCl_3$ at ambient temperature displayed four single resonances due to the CO*Me* (δ= 1.87 ppm), Ar*Me*$_2$ (δ= 2.36 ppm) and methoxy (δ= 3.76 and 3.86 ppm) protons. At about 10 °C, the resonances arising from the Ar*Me*$_2$ protons were appreciably broadened when compared to the corresponding signals at room temperature, whereas the methoxy group resonances remained unchanged. The Ar*Me*$_2$ protons coalescences near 17 °C and appeared as a fairly symmetrical line at -30 °C. The variable temperature spectra allowed calculating the free-energy barrier for the *N*-aryl bond rotation [9] in **3d** (Scheme **3**).



Scheme 3. Rotation around aryl-nitrogen single bond.

Using the expression $k=\pi\Delta\upsilon/\sqrt{2}$, first order rate constant (k= 189.3 s^{-1}) was calculated for the *N*-aryl bond rotation in **3d** at 15 °C (see Table **1**). Application of the absolute rate theory with a transmission coefficient of **3d** gave free-energy activation ($\Delta G^{\neq}$) of 58.2 ± 2 kJ.mol^{-1}, where all known sources of errors were estimated and included [10]. The experimental data available were not suitable for obtaining meaningful values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the errors in $\Delta G^{\neq}$ were not large [11]. It is necessary to mention that, measurement of different chemical shift in a series of low variable spectra was too less so that changes in first order rate constant and also the free-energy of activation are negligible in comparison with the results have been previously mentioned for -30 °C [12].

Table 1. Selected proton chemical shifts (at 500.1 MHz, in ppm, Me_4Si) and calculated activation parameters (kJ.mol^{-1}) of **3d** in $CDCl_3$ solvent.

Compd	*Temp (°C)*	*Resonance ArMe$_2$*	*Δv (Hz)*	*k (s^{-1})*	*T_C (K)*	*$\Delta G^{\neq}$ (kJ. mol^{-1})*
3d	-30	2.25 2.42	85	189.3	290	58.2±2
	25	2.36				

Experimental

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FT-IR spectrometer respectively. Also, the ^{1}H- and ^{13}C-NMR spectra were obtained from a BRUKER DRX-500 AVANCE instrument with CDCl3 as a solvent at 500.1 and 125.7 MHz respectively. In addition, the mass spectra were recorded on a Shimadzu GCMS-QP5050A mass spectrometer operating at an ionization potential of 70 eV and elemental analysis of C, H and N were performed using a Heraeus CHN-O-rapid analyzer. Dialkyl acetylenedicarboxylates, Isocyanides and acetic acid were purchased from (Merk and Fluka), and used without further purifications.

General procedure (*exemplified by* **3a**)

To a magnetically stirred solution of acetic acid (1 mmol, 0.06 g) and dimethyl acetylenedicarboxylate (1 mmol, 0.14 g) in 15 mL CH_2Cl_2 was added dropwise a solution of cyclohexyl isocyanide (1 mmol, 0.11g) in 5 mL CH_2Cl_2 at -5 °C over 10 min. Then the reaction mixture was heated to 38 °C for 4 days. After this time the solvent was removed under reduced pressure and the residues was washed with cold diethyl ether/n-hexane (3:1) as eluent.

Dimethyl-2-[N-acetyl-N-(cyclohexyl)carbamoyl]butandioate (3a)

Orange liquid oil, yield (94%). IR (in CCl_4) (ν_{max}, cm^{-1}): 1726, 1697 (C=O), 1658 (C=C). ^1H NMR (500 MHz, $CDCl_3$): 1.19-2.19 (10 H, m, 5 CH_2 of cyclohexyl), 2.33 (3 H, s, $COCH_3$), 3.56 (1 H, m, NC*H*), 3.69 and 3.77 (6 H, 2s, 2 CO_2Me), 6.54 (1 H, s, C=CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 25.09, 25.20 and 29.04 (5 C of cyclohexyl), 26.55 (CO*C*H_3), 52.18 and 52.93 (2 CO_2Me), 59.88 (N*C*H), 122.48 (*C*=CH), 143.87 (*C*=CH), 163.11 (N*C*OC=CH), 164.87 and 166.53 (2 *C*O_2Me), 174.06 (N*C*OCH_3). MS (EI, 70 eV): *m/z* (%) = 311 (M^+, 7), 2.70 (13), 252 (68), 171 (100), 140 (44), 98 (43), 59 (45), 55 (50). Anal. Calcd for $C_{15}H_{21}NO_6$ (311.33): C, 57.88; H, 6.08; N, 4.50. Found: C, 57.94; H, 6.54; N, 4.42.

Dimethyl-2-[N-acetyl-N-(benzyl)carbamoyl]butandioate (3b)

Orange oil, yield (92%). IR (in CCl_4) (ν_{max}, cm^{-1}): 1725, 1694 (C=O), 1654 (C=C). ^1H NMR (500 MHz, $CDCl_3$): 2.33 (3 H, s, $COCH_3$), 3.74 and 3.80 (6 H, 2s, 2 CO_2Me), 4.80 (2 H, br, ArCH_2), 6.69 (1 H, s, C=CH), 7.24-7.38 (5 H, m, ArH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 24.53 (CO*C*H_3), 47.60 (Ar*C*H_2N), 52.32 and 52.97 (2 CO_2Me), 123.37 (*C*=CH), 126.51, 127.61, 128.89 and 136.27 (6 C, Ar), 143.96 (*C*=CH), 162.85 (N*C*OC=CH), 165.01 and 166.71 (2 *C*O_2Me), 173.36 (N*C*OCH_3). MS (EI, 70 eV): *m/z* (%) = 319 (M^+, 1), 260 (17), 246 (13), 171 (26), 146 (53), 106 (100), 91 (93), 59 (14). Anal. Calcd for $C_{16}H_{17}NO_6$ (319.31): C, 60.18; H, 5.37; N, 4.39. Found: C, 60.23; H, 5.41; N, 4.32.

Di-tert-butyl-2-[N-acetyl-N-(benzyl)carbamoyl]butandioate (3c)

Brown liquid oil, yield (95%). IR (in CCl_4) (ν_{max}, cm^{-1}): 1717, 1710 (C=O), 1653 (C=C). ^1H NMR (500 MHz, $CDCl_3$): 1.46 and 1.51 (18 H, 2s, 2 CO_2C*Me*$_3$), 2.24 (3 H, s, $COCH_3$), 4.72 (2 H, br, ArCH_2), 6.56 (1 H, s, C=CH), 7.18-7.39 (5 H, m, ArH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 24.68 (CO*C*H_3), 27.92 and 27.97 (2 CO_2CMe_3), 47.64 (Ar*C*H_2N), 82.10 and 83.11 (2 CO_2*C*Me$_3$), 126.75 (*C*=CH), 127.50, 128.76 and 136.27 (6 C, Ar), 150.98 (*C*=CH), 161.52 (N*C*OC=CH), 163.80 and 167.34 (2 *C*O_2CMe$_3$), 172.92 (N*C*OCH_3). MS (EI, 70 eV): *m/z* (%) = 403 (M^+, 2), 385 (7), 302 (5), 231 (14), 160 (7), 148 (23), 106 (63), 91 (100), 57 (76). Anal. Calcd for $C_{22}H_{29}NO_6$ (403.47): C, 65.49; H, 7.24; N, 3.47. Found: C, 65.61; H, 7.23; N, 3.40.

Dimethyl-2-[N-acetyl-N-(2,6-dimethyphenyl)carbamoyl]butandioate (3d)

White powder, yield. (92%). mp 116-118 °C; IR (KBr) (ν_{max}, cm^{-1}): 1725, 1711 (C=O), 1655 (C=C). ^1H NMR (500 MHz, $CDCl_3$): 1.87 (3 H, s, $COCH_3$), 2.36 (6 H, s, ArMe_2), 3.76 and 3.86 (6 H, 2s, 2 CO_2Me), 6.81 (1 H, s, C=CH), 7.19 (2 H, d, *J*= 7.5 Hz, ArH), 7.26 (1 H, t, *J*= 7.5 Hz, ArH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 17.89 (ArMe_2), 24.05 (CO*C*H_3), 52.26 and 52.74 (2 CO_2Me), 125.12 (*C*=CH), 129.16, 129.41, 135.48 and 136.84 (6 C, Ar), 143.38 (*C*=CH), 163.17 (N*C*OC=CH), 164.49 and 164.69 (2 *C*O_2CMe$_3$), 173.07 (N*C*OCH_3). MS (EI, 70 eV): *m/z* (%) = 333 (M^+, 27), 302 (13), 274 (73), 216 (29), 200 (100), 146 (73), 120 (42), 105 (47), 91 (44) 59 (87). Anal. Calcd for $C_{17}H_{19}NO_6$ (333.34): C, 61.25; H, 5.75; N, 4.20. Found: C, 61.48; H, 5.76; N, 4.11.

Diethyl-2-[N-acetyl-N-(2,6-dimethyphenyl)carbamoyl]butandioate (3e)

White powder, yield (93%). mp 68-70 °C; IR (KBr) (ν_{max}, cm^{-1}): 1719, 1695 (C=O), 1648 (C=C). ^1H NMR (500 MHz, $CDCl_3$): 1.28 and 1.34 (6 H, 2t, *J*= 7.1 Hz, $CO_2CH_2CH_3$), 1.86 (3 H, s, $COCH_3$), 2.37 (6 H, s, ArMe_2), 4.21 and 4.34 (4 H, 2q, *J*= 7.1 Hz, 2 $CO_2CH_2CH_3$), 6.81 (1 H, s, C=CH), 7.18 (2 H, d, *J*= 7.4 Hz, ArH), 7.25 (1 H, t, *J*= 7.4 Hz, ArH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.05 and 14.12 (2 OCH_2CH_3) 18.04 (ArMe_2), 24.05 (CO*C*H_3), 61.26 and 62.00 (2 OCH_2CH_3), 125.61 (*C*=CH), 129.10, 129.35, 135.56 and 136.91 (6 C, Ar), 143.57 (*C*=CH), 162.80 (N*C*OC=CH), 164.31 and 164.65 (2 *C*O_2Et), 172.95 (N*C*OCH_3). MS (EI, 70 eV): *m/z* (%) = 361 (M^+, 20), 319 (10), 288 (60), 274 (29), 246 (47), 244 (43), 200 (54), 171 (27), 143 (100). Anal. Calcd for $C_{19}H_{23}NO_6$ (361.39): C, 63.15; H, 6.41; N, 3.88. Found: C, 63.27; H, 6.30; N, 3.95.

Di-tert-butyl-2-[N-acetyl-N-(2,6-dimethyphenyl) carbamoyl]butandioate (3f)

Pale white powder, yield (90%). mp 115-117 °C; IR (KBr) (ν_{max}, cm^{-1}): 1723, 1694 (C=O), 1638 (C=C). ^1H NMR (500 MHz, $CDCl_3$): 1.46 and 1.54 (18 H, 2s, 2 CO_2CMe_3), 1.85 (3 H, s, $COCH_3$), 2.36 (6 H, s, $ArMe_2$), 6.63 (1 H, s, C=CH), 7.16 (2 H, d, *J*= 7.5 Hz, ArH), 7.24 (1 H, t, *J*= 7.5 Hz, ArH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 18.21 ($ArMe_2$), 24.13 ($COCH_3$), 27.99 and 28.05 (2 CO_2CMe_3), 81.81 and 83.03 (2 CO_2CMe_3), 126.86 (*C*=CH), 128.97, 129.18, 135.73 and 137.10 (6 C, Ar), 144.15 (*C*=CH), 162.09 (N*C*OC=CH), 163.77 and 165.11 (2 CO_2CMe_3), 172.62 (N*C*OCH_3). MS (EI, 70 eV): *m/z* (%) = 418 (M^++1, 8), 417 (M^+, 23), 344 (7), 316 (42), 260 (100), 200 (17), 163 (46), 146 (33), 105 (12), 91 (5), 77 (9), 57 (71). Anal. Calcd for $C_{23}H_{31}NO_6$ (417.50): C, 66.17; H, 7.48; N, 3.35. Found: C, 66.25; H, 7.57; N, 3.28.

References

[1] Laszlo, P. *In Organic Reactions*: *Simplicity and Logic*, (Wiley, New York), 1995.

[2] Timmons, C.; Kattuboina, A.; Banerjee, S.; Li, G. *Tetrahedron*, **2006**, *62*, 7151.

[3] (a) Nair, V.; Vinod, A. U.; Somarajan-Nair, J.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett*, **2000**, *41*, 6675. (b) Nair, V.; Vinod, A. U.; Abhilash, N.; Menon, R. S.; Santhi, V.; Varma, R. L.; Viji, S.; Mathew, S.; Srinivas, R.; *Tetrahedron*, **2003**, *59*, 10279. (c) Esmaeili, A. A.; Darbaniani, M. *Tetrahedron*, **2003**, 59, 5545. (d) Yavari, I.; Hazeri, N.; Maghsoodlou, M. T.; Zabarjad-Shiraz, N. *Monatsh Chem*, **2001**, *132*, 683. (e) Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Hazeri, N.; Marandi, G.; Bijanzadeh, H. R.; *J. Chem. Res*, **2006**, 73. (f) Hazeri, N.; Habibi-Khorassani, S. M.; Maghsoodlou, M. T.; Marandi, G.; Nassiri, M.; Ghulame-Shahzadeh, A. *J. Chem. Res*, **2006**, 185. (g) Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Marandi, G.; Nassiri, M.; *Synth Commun*, **2005**, *35*, 2771. (h) Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Marandi, G.; Khandan-Barani, K.; Ziyaadini, M.; Aminkhani, A.; *Arkivoc*, **2007**, (*i*), 173. (i) Alizadeh, A.; Rostamnia, S.; Zhu, L. G. *Tetrahedron*, **2006**, *62*, 5641. (j) Alizadeh, A.; Rostamnia, S.; Esmaili, A. A.; *Synthesis*, **2007**, *5*, 709. (k) Alizadeh, A.; Rostamnia, S.; Hu, M. L. *Synthesis*, **2006**, *10*, 1592.

[4] Ugi, I. *Isonitrile Chemistry*, (Academic Press, London), 1971.

[5] Ugi I, *Angew. Chem., Int. Ed. Engl*, **1982**, *21*, 810.

[6] Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed*, **2000**, *39*, 3168.

Conclusions

In conclusion, we have prepared novel dialkyl-2-[*N*-acetyl-*N*-(alkyl or aryl)carbamoyl]butandioate derivatives via one-pot reaction between isocyanides and acetic acid in the presence of dialkyl acetylenedicarboxylates. The present reaction is performed under neutral conditions and starting materials and reagent can be reacted without any prior activation.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the University of Sistan & Balouchestan.

[7] Baker, R. H.; Stanonis, D. *J. Am. Chem. Soc*, **1951**, *73*, 699.

[8] Bock, H.; Ugi, I. *J. Prakt. Chem*, **1997**, *339*, 835.

[9] Cervinka, O. *The Chemistry of Enamines*, Edited by Z Roppoport, (Wiley, New York), 1994, Part.1, p. 219.

[10] Gunther, H. *NMR Spectroscopy*, 2ed ed, (Wiley, New York), 1995, Capter 9.

[11] Anet, F. A. L.; Anet, R. *Dynamic Nuclear Maghnetic Resonance Spectroscopy*, Edited by Cotton, F. A.; Jackman, L. M. (Academic Press, New York), 1975, Chapter 8.

[12] Oki, M. *Application of Dynamic NMR Spectroscopy to Organic Chemistry*, Edited by (VCH publishers), 1985.