Three-Component One-Pot Synthesis of Functionalized 1,2,3,6-Tetrahydropyrano[4,3-b]pyrroles

Issa Yavari,*a,b Manzarbano Esnaasharia

a Department of Chemistry, Science & Research Campus, Islamic Azad University, Ponak, Tehran, Iran
b Department of Chemistry, Tarbiat Modarres University, PO Box 14115-175, Tehran, Iran
Fax +98(21)8006544; E-mail: yavarisa@modares.ac.ir
Received 6 December 2004

SYNTHESIS 2005, No. 7, pp 1049–1051
Advanced online publication: 09.03.2005
DOI: 10.1055/s-2005-861839; Art ID: P14604SS
© Georg Thieme Verlag Stuttgart · New York

Abstract: The reactive 1:1 adduct, produced from the reaction between dialkyl acetylenedicarboxylates and 2,6-dimethylphenyl isocyanide, was trapped by methyl 2,4-dioxopentanoate to yield dialkyl 1-(2,6-dimethylphenyl)-4-methyl-2,3-dioxo-1,2,3,6-tetrahydropyrano[4,3-b]pyrrole-6,7-dicarboxylates in moderate yields.

Key words: three component reaction, Ugi reaction, methyl 2,4-dioxopentanoate, 2,6-dimethylphenyl isocyanide, acetylenic esters

Isocyanides are compounds with an extraordinary functional group; its unusual valence structure and reactivity were discussed for over one and a half centuries.1 Isocyanides are the only class of stable organic compounds with a formally divalent carbon. Owing to its reactivity the isocyanide group differs fundamentally from other functional groups.

One of the classic themes in the chemistry of isocyanides is heterocyclic synthesis.2,3 Among others, useful syntheses of oxazolines,4 pyroles,5 imidazoles,6 oxazoles,7 and thiazoles8 have been described. In continuation of our interest in the application of isocyanides in heterocyclic synthesis,9,10 we now report the reaction between dialkyl acetylenedicarboxylates 1 and 2,6-dimethylphenyl isocyanide in the presence of methyl 2,4-dioxopentanoate.11 This three-component one-pot synthesis leads to highly functionalized dialkyl 1-(2,6-dimethylphenyl)-4-methyl-2,3-dioxo-1,2,3,6-tetrahydropyrano[4,3-b]pyrrole-6,7-dicarboxylates 2a–c (Scheme 1).

Scheme 1

2,6-Dimethylphenyl isocyanide and acetylenic esters 1 in the presence of methyl 2,4-dioxopentanoate undergo a smooth reaction in CH2Cl2 at room temperature to produce compounds 2a–c in moderate yields. A single-crystal X-ray diffraction study confirmed the identity of compound 2e.12 An ORTEP diagram of 2e is shown in Figure 1.

The mass spectra of these compounds are fairly similar and display molecular ion peaks. Any initial fragmentation involved the loss of the ester moieties. The 1H NMR spectrum of compound 2a exhibited six single sharp lines, readily recognized as arising from methyl (δ = 2.10, 2.12, and 2.67), methoxy (δ = 3.06 and 3.79), and methine (δ = 5.96) protons, together with a fairly complex multiplet in the aromatic region. The 13C NMR spectrum of 2a showed twenty signals in agreement with the proposed 1,2,3,6-tetrahydropyrano[4,3-b]pyrrole structure. The 15N NMR spectrum exhibited a signal at δ = 155.8, downfield from external liquid ammonia, for the lactam nitrogen atom. The observed 15N shift for 2a is in good agreement with the previously reported values for lactams.13 The 1H and 13C NMR spectra of 2b and 2c are similar to those of 2a except for the ester groups, which exhibit characteristic signals with appropriate chemical shifts.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate 3 between 2,6-dimethylphenyl isocyanide and the acetylenic ester. Protonation of 3 by methyl 2,4-dioxopentanoate leads to the formation of a reactive 1:1 adduct 4, which is trapped by methyl 2,4-dioxopentanoate to yield 2a–c in moderate yields.
tanoate and subsequent attack of the resulting nucleophile generated to the positively charged ion 4 affords 5. This intermediate first loses methanol to give the pyrrole derivative 6. The heterotriene moiety of 6 undergoes an electrocyclic ring closure, under the reaction conditions employed, giving the 1,2,3,6-tetrahydropyrano[4,3-b]pyrrole derivative 2 (Scheme 2). Such a cyclization reaction is not unprecedented.\cite{14,15}

The noteworthy feature of the $1^H$ and $13^C$ NMR spectra of 2a–c is the presence of two separate signals for the ArCH$_3$ groups. The $1^H$ NMR spectrum of 2a in 1,2-dichlorobenzene at 330 K showed that the resonances arising from the ArCH$_3$ ($\delta = 2.10$ and 2.12) protons were appreciably broadened when compared to the same signals in the spectrum measured at room temperature. These signals coalesced near 405 K and appeared as a fairly sharp symmetrical resonance at 430 K. This dynamic NMR effect is interpreted in terms of a restricted rotation around the Ar–N bond.

Although an extensive line shape analyses in relation to the dynamic NMR effect observed for 2a was not undertaken in the present work, the variable temperature spectra allowed the calculation of the free energy barrier (if not the enthalpy or entropy of activation) for the dynamic NMR process in 2a. From coalescence of the signals attributed to the ArCH$_3$ protons and using the expression $k = \pi \Delta \nu / 2$, we calculate that the first-order rate constant ($k$) for the dynamic NMR effect in 2a to be 130 s$^{-1}$ at 405 K. Application of the absolute rate theory with a transmission coefficient of 1 gives a free-energy of activation ($\Delta G^*$) of 88 + 2 kJ mol$^{-1}$ for 2a, where all known sources of errors are estimated and included.\cite{16} The experimental data available are not suitable for obtaining meaningful values of $\Delta H^*$ and $\Delta S^*$, even though the errors in $\Delta G^*$ are not large.\cite{17}

The presented reaction provides a simple entry to the synthesis of dialkyl 1-(2,6-dimethylphenyl)-4-methyl-2,3-dioxo-1,2,3,6-tetrahydropyrano[4,3-b]pyrrole-6,7-dicarboxylates of potential synthetic interest.

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The NMR spectra were recorded at 300 ($1^H$), 75 ($13^C$), and 30 ($15^N$) MHz on a Bruker Avance DPX-300 MHz NMR instrument with CDCl$_3$ as solvent. Chemical shifts ($\delta$) are reported relative to TMS as the internal standard. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification.

**Dimethyl 1-(2,6-Dimethylphenyl)-4-methyl-2,3-dioxo-1,2,3,6-tetrahydropyrano[4,3-b]pyrrole-6,7-dicarboxylate (2a); Typical Procedure**

To a stirred solution of methyl 2,4-dioxopentanoate (0.29 g, 2 mmol), and dimethyl acetylenedicarboxylate (1a; 0.28 g, 2 mmol) in CH$_2$Cl$_2$ (10 mL) was added dropwise, a solution of 2,6-dimethylphenyl isocyanide (0.26 g, 2 mmol) in CH$_2$Cl$_2$ (4 mL) at 0 °C over 5 min. The reaction mixture was then allowed to stay at r.t. for 48 h. The solvent was removed under reduced pressure and the viscous residue was purified by preparative TLC on silica gel (Merck silica gel DC-Fertigplatten 60/Kieselgur F$_{254}$) 20 × 20 cm plates using a mixture of CHCl$_3$ and EtOAc (10:1) as eluent. Zones were detected by quenching of indicator fluorescence upon exposure to 366 nm UV light. The product was obtained by extraction of the silica gel with CH$_2$Cl$_2$ and evaporation of CH$_2$Cl$_2$ to afford yellow crystals (from 1:1 n-hexane–EtOH; yield: 0.48 g (63%); mp 146–148 °C. IR (KBr): 1739 and 1681 (C=O), 1613 (C=C), 1230 and 1218 cm$^{-1}$ (C–O).

**Scheme 2**
Yield: 0.58 g (62%); yellow crystals (from 1:1 hexane–EtOH); mp 120–122 °C.

Diethyl 1-(2,6-Dimethylphenyl)-4-methyl-2,3-dioxo-1,2,3,6-tetrahydropyran-4,3-b]pyrrole-6,7-dicarboxylate (2b)

MS (EI 70 eV): m/z (%) = 470 (M⁺ + 1, 8), 469 (40), 411 (71), 360 (41), 304 (37), 248 (55), 57 (100), 41 (72).

Anal. Calcd for C₂₆H₃₁NO₇ (469.5): C, 66.56; H, 6.67; N, 2.98. Found: C, 66.56; H, 6.70; N, 2.92%.

References

(11) Methyl 2,4-dioxopentanoate, which is apparently completely enolized in the liquid phase, was prepared based on the literature procedure for the ethyl ester: Marvel, C. S.; Dreger, E. E. Org. Synth. Coll. Vol. 1 1941, 238.
(12) Crystallographic data for 2c: C₉₂H₇₀NO₆, F₆, = 469.52, monoclinic, space group P2₁/c, Z = 8, a = 9.6290 (10) Å, b = 25.076 (2) Å, c = 20.546 (2) Å, α = 90°, β = 93.822 (3)°, γ = 90°, V = 4945.7 (8) Å³, ρcalc = 1.261 g/cm³, R1 = 0.060, wR2 = 0.1240, –6 ≤ h ≤ 12; –16 ≤ k ≤ 20; –26 ≤ l ≤ 24; Mo-kα (λ = 0.7107 Å), Τ = 110 (2) K. The structure factors are available from the author upon request.