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A Facile Route to Highly Functionalized Ketenimines

I. Yavari[1,*], M. Davar-Panah[1], M. Heydari[2], K. Najafian[2], and A. Zonouzi[1]

[1] Chemistry Department, Tarbiat Modarres University, Tehran, Iran
[2] Chemistry Department, Science and Research Branch, Islamic Azad University, Tehran, Iran

Summary. A one-pot synthesis of highly functionalized ketenimines by reaction of alkyl isocyanides with dialkyl acetylenedicarboxylates in presence of 1,3-diphenylpropan-1,3-dione is reported.

Keywords. Ketenimines; Alkyl isocyanides; Acetylenic esters; CH-Acids.

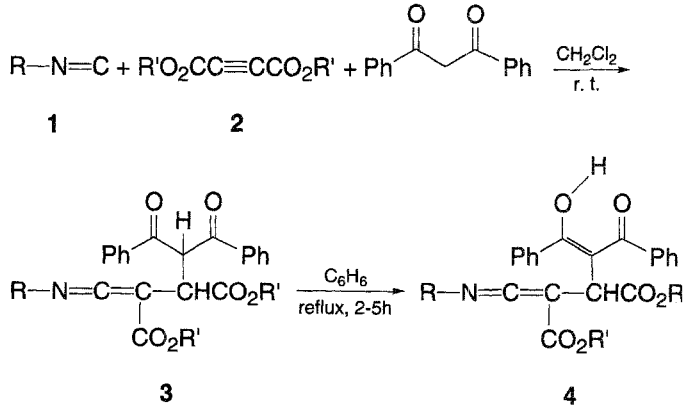
Ein einfacher Weg zu hochfunktionalisierten Keteniminen

Zusammenfassung. Es wird eine Eintopfsynthese hochfunktionalisierter Ketenimine durch Reaktion von Isocyaniden mit Dialkylacetylendicarboxylaten in Gegenwart von 1,3-Diphenylpropan-1,2-dion beschrieben.

Introduction

In recent years, ketenimines have attracted interest as dehydrating agents for peptide synthesis, as complexing agents for transition metal ions, and as co-reagents for *DMSO* oxidations [1, 2]. They have also found widespread use as reactive starting materials for the generation of four-, five-, and six-membered heterocyclic ring systems [3–6]. The spectroscopic properties of ketenimines have been intensively investigated [7, 8].

We here describe a reaction of alkyl isocyanides (**1**) with dialkyl acetylenedicarboxylates (**2**) in presence of 1,3-diphenylpropan-1,3-dione. This three-component condensation reaction produces highly functionalized ketenimines **3** in fairly good yields. These are converted quantitatively to their enol tautomers **4** upon refluxing in benzene.



3,4	R	R′
a	^{t}Bu	Me
b	Cyclohexyl	Me
c	Cyclohexyl	Et
d	Cyclohexyl	^{t}Bu

Results and Discussion

On the basis of the well established chemistry of isocyanides [9–12] it is reasonable to assume that compound **3** results from the initial addition of the alkyl isocyanides to the acetylenic ester and a concomitant protonation of the 1:1 adduct by 1,3-diphenylpropan-1,3-dione. Then, the positively charged ion is attacked by the enolate anion of the diketone to form ketenimines **3**.

The structures of compounds **3a–d** were deduced from their elemental analyses and their ^{1}H NMR and IR spectra. The nature of these compounds as 1:1:1 adducts was apparent from the mass spectra which displayed molecular ion peaks at $m/z = 449$, 475, 503, and 559. Initial fragmentations involve loss of the ketenimine side chains (R′OH, CO_2R', PhCOCHCOPh, PhCO, C_6H_5).

The ^{1}H NMR spectrum of **3a** exhibited three single sharp lines arising from *tert*-butyl ($\delta = 1.4$ ppm) and methoxy ($\delta = 3.6$ and 3.7 ppm) protons along with two sharp doublets ($\delta = 4.5$ and 6.4 ppm, $J = 11.1$ Hz) for the two vicinal CH groups. The aromatic protons appear as a multiplet at $\delta = 7.3$–8.2 ppm [13].

The ^{1}H NMR spectra of **3b**, **3c**, and **3d** are similar to that of **3a**, except for the signals of the cyclohexyl and ester groups. The cyclohexyl moieties of compounds **3b–d** appear as a complex multiplet at $\delta = 1.1$–1.9 ppm for the methylene groups and a broad unstructured multiplet centered at about $\delta = 3.6$ ppm for the methin group. The ester groups exhibit characteristic signals with appropriate chemical shifts (see Experimental).

Compounds **3a–d** can be converted quantitatively to their enol tautomers **4a–d** upon refluxing in benzene for 2–5 h. The ^{1}H NMR spectra of **4a–d** are similar to those of the corresponding keto forms except for the two doublets which now appear as a single sharp line (for example, at $\delta = 4.65$ ppm for **4b**) and a fairly broad peak at $\delta = 14.9$ ppm (for **4b**), indicating extensive intramolecular hydrogen bonding.

The structural assignments of compounds **3** and **4** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest are the strong ketenimine absorption band at about 2060 cm^{-1} in all compounds and a broad OH peak at about 3400 cm^{-1} for the enol tautomers **4a–d**.

In summary, the reaction of alkyl isocyanides with electron deficient acetylenic esters in the presence of 1,3-diphenylpropan-1,3-dione provides a simple one-pot entry into the synthesis of polyfunctionalized ketenimines of potential synthetic interest.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Shimadzu FT-IR-4300 spectrophotometer as KBr discs. ^{1}H NMR spectra were measured at 80 MHz with an AC-80 Bruker NMR spectrometer ($CDCl_3$, *TMS* as internal standard).

Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV.

Preparation of Dimethyl-1-(N-cyclohexyliminomethylidene)-2-(dibenzoylmethyl)-succinate (**3b**) *and* (**4b**); *General Procedure*

To a magnetically stirred solution of dimethyl acetylenedicarboxylate (0.71 g, 5 mmol) and 1,3-diphenylpropan-1,3-dione (1.12 g, 5 mmol) in dichloromethane (10 ml), a mixture of cyclohexyl isocyanide (0.55 g, 5 mmol) in dichloromethane (2 ml) was added dropwise at 0 °C over 5 min. The reaction mixture was then allowed to warm up to 20 °C and stirred for 2 h. After 24 h in a refrigerator at 5 °C, pale yellow crystals of dimethyl-1-(N-cyclohexyliminomethylidene)-2-(dibenzoylmethyl)-succinate (**3b**, 0.9 g, m.p.: 88–90 °C, 40%) were collected by filtration. IR (KBr): ν_{max} = 2060 (N=C=C), 1735 and 1710 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.1–2.1 (10H, m, $5CH_2$), 3.24 and 3.47 (6H, 2s, $2CH_3O$), 3.52 (1H, m, cyclohexyl CH), 4.95 (1H, d, J = 10.5 Hz, $CH(COPh)_2$), 6.22 (1H, d, J = 10.5 Hz, C=C–CH), 7.2–8.2 (10H, m, $2C_6H_5$) ppm; MS: m/z (%) = 475 (M^+, 25), 443 (M^+-CH_3OH, 40), 416 (M^+-CO_2Me, 70), 224 ($PhCOCHCOPh^+$, 30), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$, 60); calc. for $C_{28}H_{29}ON_6$ (475.51): C, 70.72, H, 6.15, N, 2.94; found: C, 67.3, H, 6.2, N, 2.7.

Dimethyl-1-(N-t-butyliminomethylidene)-2-(dibenzoylmethyl)-succinate (**3a**)

M.p.: 56–58 °C; yield: 65%; IR (KBr): ν_{max} = 2061 (N=C=C), 1739 and 1697 (C=O), 1597 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.41 (9H, s, ^tBu), 3.62, 3.73 (6H, 2s, $2CH_3O$), 4.54 (1H, d, J = 10.1 Hz, $CH(COPh)_2$), 6.41 (1H, d, J = 11.1 Hz, C=C–CH), 7.3–8.2 (10H, m, $2C_6H_5$) ppm; MS: m/z (%) = 449 (M^+, 12), 417 (M^+-MeOH, 22), 392 (M^+, ^tBu, 51), 224 ($PhCOCHCOPh^+$, 35), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$, 51); calc. for $C_{26}H_{27}NO_6$ (449.48): C, 69.47, H, 6.06, N, 3.11; found: C, 70.1, H, 5.9, N, 3.2.

Diethyl-1-(N-cyclohexyliminomethylidene)-2-(dibenzoylmethyl)-succinate (**3c**)

M.p.: 72–73 °C; yield 48%; IR (KBr): ν_{max} = 2064 (N=C=C), 1741 and 1677 (C=O), 1598 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.1–2.1 (10 H, m, cyclohexyl CH), 4.12 and 4.30 (4H, 2q, J = 7.12 Hz, $2OCH_2$), 4.87 (1H, d, J = 10.2 Hz, $CH(COPh)_2$), 6.33 (1H, d, J = 10.2 Hz, C=C–CH), 7.2–8.2 (10H, m, $2C_6H_5$) ppm; MS: m/z (%) = 503 (M^+, 3), 430 (M^+-CO_2Et, 10), 224 ($PhCOCHCOPh^+$, 18), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$, 40); calc. for $C_{30}H_{33}NO_6$ (503.56): C, 71.55, H, 6.60, N, 2.78; found: C, 71.2, H, 6.8, N, 2.9.

Di-t-butyl-1-(N-cyclohexyliminomethylidene)-2-(dibenzoylmethyl)-succinate (**3d**)

M.p.: 68–69 °C; yield: 57%; IR (KBr): ν_{max} = 2060 (N=C=C), 1734 and 1691 (C=O), 1680 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.26 and 1.33 (18H, 2s, ^t2Bu), 1.1–1.8 (10 H, m, $5CH_2$), 3.6 (1H, m, cyclohexyl CH), 4.29 (1H, d, J = 10.1 Hz, $CH(COPh)_2$), 6.30 (1H, d, J = 10.1 Hz, C=C–CH), 7.1–7.9 (10H, m, $2C_6H_5$); MS: m/z (%) = 559 (M^+, 5), 224 ($PhCOCHCOPh^+$, 16), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$, 48); calc. for $C_{34}H_{41}NO_6$ (559.71): C, 72.96, H, 7.38, N, 2.50; found: C, 72.2, H, 7.5, N, 2.6.

Refluxing a benzene solution (5 ml) of **3b** (0.4 g) for 5 h produces **4b** in quantitative yield. The mass spectrum and the elemental analysis data for **4b** are similar to those for **3b**, but IR and ^1H NMR spectra are different.

Dimethyl-1-(N-t-butyliminomethylidene)-2-(Z-1-benzoyl-2-hydroxy-2-phenylethenyl)-succinate (**4a**)

M.p.: 70–72 °C; IR (KBr): ν_{max} = 3400 (OH), 2063 (N=C=C), 1738 and 1707 (C=O), 1608 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.1–2.1 (10H, m, $5CH_2$), 3.26 and 3.46 (6H, 2s, $2OCH_3$), 3.50 (1H, m, cyclohexyl CH), 4.65 (1H, s, C=C–CH), 7.2–8.2 (10H, m, $2C_6H_5$), 14.9 (1H, br s, O–H···O=C) ppm.

Dimethyl-1-(N-cyclohexyliminomethylidene)-2-(Z-1-benzoyl-2-hydroxy-2-phenylethenyl)-succinate (**4b**)

M.p.: 47–49 °C; IR (KBr): $\nu_{max} = 3405$ (OH), 2061 (N=C=C), 1740, 1701 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.40$ (9H, s, *t*Bu), 3.63 and 3.70 (6H, 2s, $2OCH_3$), 4.42 (1H, s, C=C–CH), 7.3–8.2 (10H, m, $2C_6H_5$), 14.5 (1H, br s, O–H···O=C) ppm.

Diethyl-1-(N-cyclohexyliminomethylidene)-2-(Z-1-benzoyl-2-hydroxy-2-phenylethenyl)-succinate (**4c**)

M.p.: 65–66 °C; IR (KBr): $\nu_{max} = 3420$ (OH), 2065 (N=C=C), 1743 and 1682 (C=O), 1612 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.1$–2.1 (10H, m, $5CH_2$), 1.18 and 1.35 (6H, 2t, $J = 7.12$ Hz, $2CH_3$), 3.6 (1H, m, cyclohexyl CH), 4.10 and 4.31 (4H, 2q, $J = 7.12$ Hz, $2OCH_3$), 4.62 (1H, s, C=C–CH), 7.2–8.2 (10H, m, $2C_6H_5$), 14.9 (1H, br s, O–H···O=C) ppm.

Di-t-butyl-1-(N-cyclohexyliminomethylidene)-2-(Z-1-benzoyl-2-hydroxy-2-phenylethenyl)-succinate (**4d**)

M.p.: 51–52 °C; IR (KBr): $\nu_{max} = 3420$ (OH), 2061 (N=C=C), 1730 and 1708 (C=O), 1612 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.28$ and 1.37 (18H, 2s, ^{t}Bu), 1.1–1.9 (10H, m, $5CH_2$), 3.6 (1H, m, cyclohexyl CH), 4.11 (1H, s, C=C–CH), 7.1–7.9 (10H, m, $2C_6H_5$), 14.8 (1H, br s, O–H···O=C) ppm.

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