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A novel four-component reaction of diethylamine, an aromatic aldehyde and an alkyl isocyanide with dialkyl acetylenedicarboxylates in the presence of silica gel: an efficient route for the regio- and stereoselective synthesis of sterically congested alkenes

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Abstract—The 1:1 intermediate generated by the addition of an isocyanide to a dialkyl acetylenedicarboxylate is trapped by the iminium ion intermediate that forms from the reaction between an aromatic aldehyde and diethylamine. The reactions were completed in the presence of silica gel powder. The product dialkyl 2-[(alkylamino)carbonyl]-3-[(*Z*)-1-(diethylamino)-1-arylmethylidene]succinates, were produced in acceptable yields. The reactions are completely regio- and stereoselective.

1. Introduction

Multicomponent reactions (MCRs) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[1–3] In 1921, Passerini[4] pioneered the use of isocyanides and successfully developed a three-component synthesis of α-acyloxycarboxamides by reaction of a carboxylic acid, an aldehyde, and an isonitrile.[5] However, the most important breakthrough came in 1959 when Ugi described a four-component synthesis of α-acylamino amides from an aldehyde, an amine, an acid and an isocyanide.[6,7] This reaction, named after Ugi (Ugi 4CR or U-4CR) has become a widely investigated transformation during the past decade, in conjunction with technologies such as high throughput screening and combinatorial chemistry.[8–14]

The ability of an isonitrile to undergo easy R-addition with a nucleophile and an electrophile under mild conditions has made them popular reactants for the development of novel MCRs.[15] Isocyanides,[16] regarded for many years as compounds with unpleasant odors and with very few chemical and pharmaceutical applications, are now looked upon as useful synthons, attributed primarily to the renaissance of the isocyanide based multicomponent,[8,17] Passerini three-component (P-3CR),[18,19] and more importantly, the Ugi four-component reaction (U-4CR).[6,7,20]

MCRs involving diisopropylaminoisocyanide and dimethyl acetylenedicarboxylate (DMAD) have been investigated.[21–32] In 1969, Winterfeldt et al. described the reaction of isocyanides and acetylene compounds.[33] The chemistry is based upon the initial formation of a zwitterionic adduct of the isocyanide with the acetylene (Scheme 1).

These 1:1 intermediates have been trapped with O–H, N–H, and C–H acids,[25–35] but not with iminium ions. We have now developed a convenient preparation of densely functionalized alkenes **6** using a simple one-pot[36–46] four-component reaction between dialkyl acetylenedicarboxylates and isocyanides with iminium ions generated from aromatic aldehydes and diethylamine in the presence of silica gel. The reaction occurs

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Keywords: Silica gel; Multicomponent reaction; Isocyanide; Aldehyde; Acetylenic ester.

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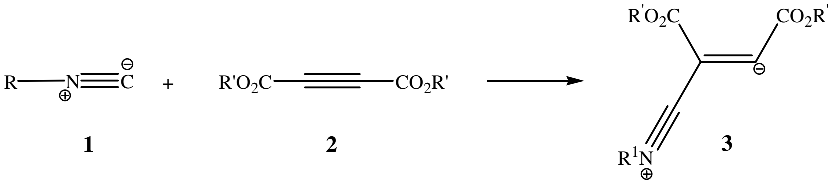
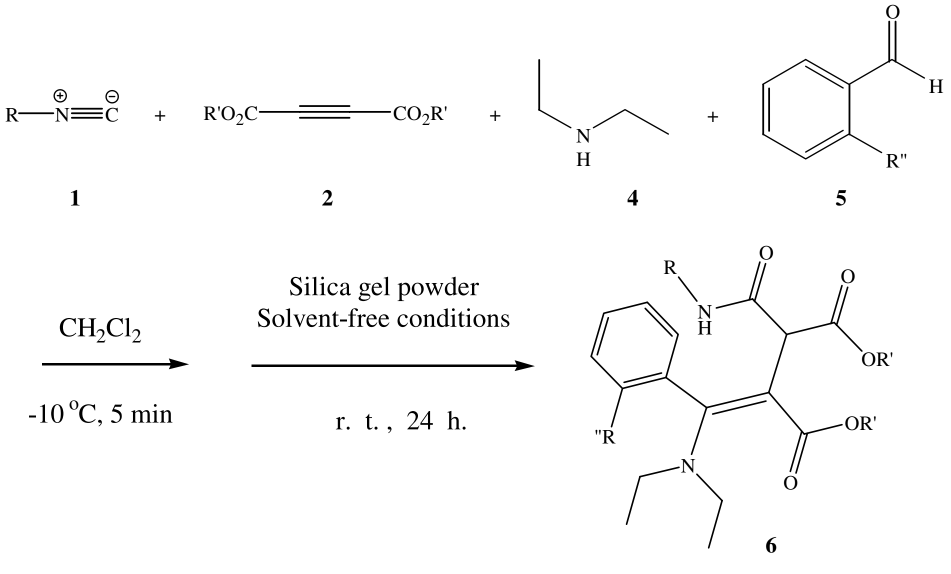


Scheme 1. Dialkyl acetylenedicarboxylates and isocyanides form initial zwitterionic species **3**.

smoothly in the presence of silica gel at ambient temperature, to produce dialkyl 2-[(alkylamino)carbonyl]-3-[(*Z*)-1-(diethylamino)-1-arylmethylidene]succinates **6** in 48–80% yields (Scheme 2).

2. Results and discussion

The structures of compounds **6a–f** were deduced from their IR, and high-field ^{1}H and ^{13}C NMR spectra, and by mass spectrometry. For example, the IR spectrum of **6a** shows a strong absorption at 3408 cm^{-1} indicating the presence of an amide, and sharp bands at 1746, 1692 and 1577 cm^{-1} were assigned to the two ester carbonyls and the amide carbonyl, respectively. The ^{1}H NMR spectrum of **6a** exhibited 11 signals readily recognized as arising from a tetramethylbutyl group ($\delta = 0.82$ (s, CMe_3); δ 1.35 and 1.37 (2 s, CMe_2NH); δ 1.58 and 1.73 (2 d, $^2J_{\mathrm{HH}} = 15.0$ Hz, CH_2CMe$_3$), two ethyl ($\delta = 1.16$ and 3.16, $^3J_{\mathrm{HH}} = 7.3$ Hz) and two methoxy groups ($\delta = 3.61$ and 3.91) along with an aliphatic CH ($\delta = 4.59$ ppm) and an amide hydrogen atom ($\delta = 6.75$ ppm), exchangeable with D$_2$O. The presence of diastereotopic groups (CH_AH_BCMe$_3$ and CMe_A-Me_BNH) in the tetramethylbutyl moiety resulted from the existence of a stereogenic center (aliphatic CH) in **6a**. The phenyl group gave rise to characteristic signals in the aromatic region. The *Z* stereochemistry of **6a** was determined by an NOE experiment, irradiation of the aromatic protons led to an increase in the signal intensity (ca. 98%) of the aliphatic CH ($\delta = 4.59$) moiety. The ^{1}H decoupled ^{13}C NMR spectrum of **6a**



6	R	R'	R"	% Yield
a	1,1,3,3-Tetramethylbutyl	Me	NO$_2$	77
b	1,1,3,3-Tetramethylbutyl	Et	NO$_2$	80
c	1,1,3,3-Tetramethylbutyl	Me	H	48
d	1,1,3,3-Tetramethylbutyl	Et	H	57
e	Cyclohexyl	Me	H	48
f	Cyclohexyl	Et	H	51

Scheme 2.

showed 22 resonances, for example, the two vinylic carbons and the aliphatic carbon (CH) were observed at δ 82.87, 153.78, and 67.98 ppm, respectively.

The ^{1}H and ^{13}C NMR spectra of compounds **6b–f** were similar to those of **6a**, except for the aromatic moiety, and the ester groups, which exhibited characteristic signals with appropriate chemical shifts.

3. Conclusions

In summary, the reaction between the zwitterionic intermediate generated from dialkyl acetylenedicarboxylates and isocyanides with iminium ion intermediates formed from aromatic aldehydes and diethylamine in the presence of silica gel leads to dialkyl 2-[(alkylamino)-carbonyl]-3-[(*Z*)-1-(diethylamino)-1-arylmethylidene]succinates via a one-pot, four-component regio- and stereoselective process.

4. General procedure for preparation of compound 6a–f

A mixture of diethylamine (0.10 ml, 1 mmol) and benzaldehyde (0.10 ml, 1 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 0.5 h. To this mixture, a solution of dimethyl acetylenedicarboxylate (0.16 ml, 1.25 mmol) and 1,1,3,3-tetramethylbutylisocyanide (0.17 ml, 1.25 mmol) in 2 mL of dry CH_2Cl_2 at -10 °C was added rapidly and the mixture stirred for 5 min at -10 °C. Silica gel powder (Merck, 1 g) was added quickly and the reaction mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was kept for 24 h at room temperature. The product was isolated by elution with dichloromethane through a short column. The solvent was removed under reduced pressure and product **6a** was obtained as a yellow viscous oil.

4.1. Dimethyl 2-[(*Z*)-1-(2-nitrophenyl)-1-(diethyl amino)methylidene]-3-{[(1,1,3,3- tetramethyl butyl)amino]carbonyl}succinate 6a

Yellow viscous oil, yield 0.39 g, 77%. IR (KBr) (υ_{max} cm^{-1}): 3408 (NH), 2962, 1746, 1692, 1577, 1454, 1377, 1223, 1162. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 0.82 (9H, s, CMe_3), 1.16 (6H, t, $^{3}J_{HH} = 7.3$ Hz, $2CH_3CH_2N$), 1.35 (3H, s, CMe_2NH), 1.37 (3H, s, CMe_2NH), 1.58 (1H, d, $^{2}J_{HH} = 15.0$ Hz, CH_2CMe_3), 1.73 (1H, d, $^{2}J_{HH} =$ 15.0 Hz, CH_2CMe_3), 3.16 (4H, q, $^{3}J_{HH} = 7.3$ Hz, CH_3CH_2N), 3.61 (3H, s, OMe), 3.91 (3H, s, OMe), 4.59 (1H, s, CH), 6.75 (1H, br s, NH, exchanged by D_2O addition), 7.40–7.47 (2H, m, C_6H_4), 7.64 (1H, d, $^{3}J_{HH} = 4.5$ Hz, $CHCC{=}C$ of C_6H_4), 7.88 (1H, d, $^{3}J_{HH} = 8.3$ Hz, $CHCNO_2$ of C_6H_4). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ_C: 12.64 (CH_3CH_2N), 28.85 and 29.00 (2 CH_3 of CMe_2NH, diastereotopic), 31.10 (3 CH_3 of CMe_3), 31.41 (C of CMe_3), 44.85 (CH_2 of CH_3CH_2N), 50.63 (OMe), 51.73 (CH_2 of CH_2CMe_3), 52.80 (OMe), 55.68 (C of CMe_2NH), 67.98 (CH), 82.87 ($C{=}CN$), 124.29, 128.85, 129.27 and 133.87 (4 CH of C_6H_4), 135.83 ($C_{ipso(C=C)}$ of C_6H_4), 148.70 ($C_{ipso(NO2)}$ of C_6H_4), 153.78 ($NC{=}C$), 166.11 (CO_2Me), 168.33 (CO_2Me), 168.95 (CONH). Anal. Calcd for $C_{26}H_{39}N_3O_7$ (505.60): C, 61.76; H, 7.77; N, 8.31. Found: C, 61.81; H, 7.80; N, 8.27.

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