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ORIGINAL PAPER

One-pot synthesis of α-hydroxyamides using alkyl isocyanides and aryl aldehydes

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Abstract A simple and efficient approach for the synthesis of α-hydroxyamides in fairly good yields by the reaction of aromatic aldehydes and alkyl isocyanides at room temperature is presented.

Keywords α-Hydroxyamide · Alkyl isocyanide · Aromatic aldehyde · One-pot synthesis

Introduction

The α-hydroxyamides are useful building blocks for the synthesis of biologically active compounds [1–6]. For example, α-hydroxyamides have been identified as inhibitors of methionine aminopeptidase-2 and as HIV protease inhibitors [7, 8]. Mycalamides are a class of α-hydroxyamides that exhibit potent antitumor activity [9]. α-Hydroxyamides are also valuable intermediates in the synthesis of natural products and various biologically active compounds [10–12]. Known methods for their preparation can be divided into four main categories: reactions of carboxylic acids and activated acid derivatives with amines, reduction of α-ketoamides, miscellaneous methods, and the synthesis of α-hydroxyamides via cyclic precursors.

The two most important isocyanide-based multicomponent reactions are the Passerini three-component reaction [13] to produce α-acyloxyamides, and the Ugi four-component reaction, which yields α-acylaminoamides. The Ugi reaction usually refers to the reaction between an amine (usually a primary or secondary amine), a carbonyl compound (aldehyde or ketone), an isocyanide, and a carboxylic acid [14].

Cyclic variations of the MCRs are also possible in which two or more components could be connected by a chain to produce heterocycles. For example, the synthesis of β-lactam rings using β-aminoacids has been known as the Ugi four-center-three-component reaction since 1961 [15].

As part of our current studies on the development of new routes to the synthesis of organic compounds and our interest in isocyanide-based reactions [16, 17], we planned to test the reaction between isocyanides and CS_2 in the presence of aryl aldehydes in CH_2Cl_2 (Scheme 1).

We found that this reaction yielded the corresponding α-hydroxyamides rather than the expected MCR product (Scheme 2). Thus, this reaction is an extension of the Passerini three-component reaction.

Results and discussion

The reaction of alkyl isocyanides **1** with aromatic aldehydes **2** in CH_2Cl_2 proceeded smoothly and had completed after three days at room temperature, affording the corresponding α-hydroxyamides **3** in fairly good yields (65–86%). ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of the α-hydroxyamides. As shown in Table 1, aromatic aldehydes containing electron-withdrawing groups gave excellent yields of the amide product **3**. The structures of the products were deduced from their elemental analyses, IR, ^1H, and ^{13}C NMR spectra. The mass spectra of compounds **3** displayed molecular ion peaks at the calculated *m/z* values. The results for the synthesis of α-hydroxyamides are given in Table 1.

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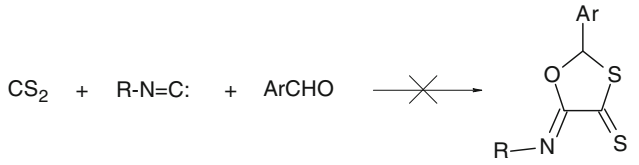
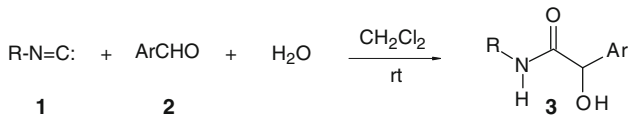


Scheme 1



Scheme 2

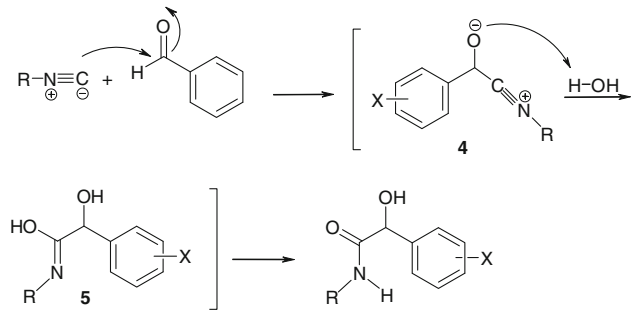
Table 1 Synthesis of α-hydroxyamides using aromatic aldehydes and alkyl isocyanides in CH_2Cl_2

Entry	Ar	R	Product	Yield / %
a	4-NO_2Ph	Cyclohexyl	**3a**	86
b	4-NO_2Ph	*tert*-Bu	**3b**	76
c	3-NO_2Ph	Cyclohexyl	**3c**	82
d	Ph	*tert*-Bu	**3d**	72
e	2,4-$(MeO)_2$Ph	Cyclohexyl	**3e**	65
f	4-BrPh	Cyclohexyl	**3f**	74
g	2,6-Cl_2Ph	Cyclohexyl	**3g**	70
h	Ph	Cyclohexyl	**3h**	68

The ^{1}H NMR spectrum of **3a** consisted of a multiplet of signals for the cyclohexyl group ($\delta = 1.05$–1.94 ppm), a broad signal for the hydroxyl group ($\delta = 3.68$–3.98 ppm), one singlet for the methine group ($\delta = 5.10$ ppm) and one signal ($\delta = 6.34$ ppm) for the N–H group, which appears as doublet ($^3J_{HH} = 7.2$ Hz), in agreement with the suggested structure. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed ten sharp signals, in agreement with the proposed structure. The characteristic signal of the C-atom in the benzylic position was observed ($\delta = 73.13$ ppm). The ^{1}H and ^{13}C NMR spectra of **3b**–**3h** are similar to those of **3a**, except for the substituted phenyl ring, which exhibited characteristic resonances with appropriate chemical shifts.

A plausible mechanism for the formation of α-hydroxyamides **3** is shown in Scheme 3. On the basis of the well-established chemistry of isocyanides [18–21], it is reasonable to assume that intermediate **4** results from the initial addition of alkyl isocyanides **1** to the carbonyl group of the aldehyde; protonation by the absorbing water then occurs, which adds hydroxide to produce intermediate **5**. This intermediate is converted to product **3** by proton transfer.

In conclusion, we have reported a general method for the synthesis of potentially interesting α-hydroxyamides from readily available aromatic aldehydes and alkyl



Scheme 3

isocyanides. The present procedure has the advantage that the reaction occurs under neutral conditions, and moreover that the substances can be mixed without any further activation or modification.

Experimental

The alkyl isocyanides, aromatic aldehydes, and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification. NMR spectra were recorded with Bruker Avance DRX-300 and DRX-500 instruments, using $CDCl_3$ as the solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constants (J) are reported in hertz (Hz). Melting points were measured with a Gallenkamp 9100 electrothermal apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. The results obtained experimentally agreed favorably with the calculated values. Mass spectra (m/z, rel%) were recorded with a Shimadzu QP-5050 GC/MS operating at an ionization potential of 70 eV. IR spectra (KBr) were measured with a Bruker Tensor 27 spectrometer.

General procedure

To a stirred solution of 0.109 g cyclohexyl isocyanide (1 mmol) in 10 cm^3 CH_2Cl_2, 0.151 g *p*-nitrobenzaldehyde (1 mmol) and 2 mmol H_2O were added in 2 cm^3 CH_2Cl_2 at room temperature over 5 min via a syringe. The reaction mixture was stirred at room temperature for three days. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Merck silica gel 60, 70–230 mesh) using hexane–ethyl acetate (8:2) as eluent. The solvent was removed under reduced pressure to afford the products **3**.

The products **3d** and **3h** are known compounds and were characterized by IR and NMR spectroscopic data, which were in agreement with those published in the literature [14].

N-Cyclohexyl-α-hydroxy-4-nitrobenzeneacetamide
(**3a**, $C_{14}H_{18}N_2O_4$)
Yellow paste, yield 0.24 g (86%); IR (KBr): $\bar{\nu}$ = 3,410, 3,319, 1,685, 1,651, 1,520, 1,346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.94 (10H, m, $5CH_2$), 3.69 (1H, m, N–CH), 3.68–3.98 (1H, br s, OH), 5.10 (1H, s, CH), 6.34 (1H, d, $^3J_{HH}$ = 7.2 Hz, NH), 7.61 (2H, d, $^3J_{HH}$ = 8.9 Hz, CH_{ar}), 8.19 (2H, d, $^3J_{HH}$ = 8.7 Hz, CH_{ar}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.67 ($2CH_2$), 25.33 (CH_2), 32.82 ($2CH_2$), 48.52 (N–CH), 73.13 (CH), 123.77 ($2CH_{ar}$), 127.36 ($2CH_{ar}$), 146.68, 147.81 ($2C_{ar}$), 169.80 (C=O) ppm; MS (EI, 70 eV): *m/z* = 279 (0.8), 186 (9), 153 (100), 136 (29), 106 (12), 83 (32), 55 (27).

N-tert-Butyl-α-hydroxy-4-nitrobenzeneacetamide
(**3b**, $C_{11}H_{13}N_2O_4$)
Yellow powder, yield 0.18 g (76%); m.p.: 156–158 °C; IR (KBr): $\bar{\nu}$ = 3,385, 1,655, 1,524, 1,350 cm^{-1}; 1H NMR (500 MHz, CDCl3): δ = 1.37 (9H, s, CMe3), 3.61 (1H, d, $^3J_{HH}$ = 4.2 Hz, OH), 5.10 (1H, d, $^3J_{HH}$ = 4.0 Hz, CH), 6.01 (1H, br s, NH), 7.66 (2H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH arom), 8.28 (2H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH arom) ppm; 13C NMR (125.7 MHz, $CDCl_3$): δ = 28.51 (CMe_3), 52.34 (CMe_3), 73.23 (CH), 123.74 (2CH-arom), 127.38 (2CH-arom), 146.69, 147.79 (2C-arom), 169.71 (C=O) ppm; MS (EI, 70 eV): *m/z* = 259 (4), 215 (2), 172 (4), 160 (5), 152 (100), 136 (43), 119 (9), 104 (20), 77 (8), 57 (60).

N-Cyclohexyl-α-hydroxy-3-nitrobenzeneacetamide
(**3c**, $C_{14}H_{18}N_2O_4$)
Pale yellow paste, yield 0.23 g (82%); IR (KBr): $\bar{\nu}$ = 3,385, 3,310, 1,655, 1,649, 1,524, 1,348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.91 (10H, m, $5CH_2$), 3.72 (1H, m, N–CH), 3.81–3.95 (1H, br s, OH), 5.14 (1H, s, CH), 6.33 (1H, br s, NH), 7.54 (1H, t, $^3J_{HH}$ = 8.1 Hz, CH_{ar}), 7.79 (1H, d, $^3J_{HH}$ = 7.5 Hz, $2CH_{ar}$), 8.18 (1H, d, $^3J_{HH}$ = 8.1 Hz, CH_{ar}), 8.32 (1H, s, CH_{ar}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.71, 25.36, 32.87 ($5CH_2$), 48.57 (N–CH), 73.02 (CH), 121.46, 123.36, 129.66, 132.82 ($4CH_{ar}$), 141.72, 148.38 ($2C_{ar}$), 169.74 (C=O) ppm.

N-Cyclohexyl-α-hydroxy-2,4-dimethoxybenzeneacetamide
(**3e**, $C_{16}H_{23}NO_4$)
Viscous oil, yield 0.19 g (65%); IR (KBr): $\bar{\nu}$ = 3,325, 1,657, 1,523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.92 (10H, m, $5CH_2$), 3.73 (1H, m, N–CH), 3.69–3.81 (1H, br, OH), 4.21 (3H, s, OCH_3), 4.25 (3H, s, OCH_3), 5.15 (1H, s, CH), 6.90 (1H, br s, NH), 6.21 (1H, s, CH_{ar}), 6.26 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ar}), 6.97 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ar}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.72, 25.34, 32.76 ($5CH_2$), 48.52 (N–CH), 56.10, 56.31 ($2OCH_3$), 73.12 (CH), 101.02, 107.14, 113.79, 131.76, 161.85, 163.41 ($6C_{ar}$), 170.67 (C=O) ppm.

4-Bromo-N-cyclohexyl-α-hydroxybenzeneacetamide
(**3f**, $C_{14}H_{18}BrNO_2$)
Pale yellow paste, yield 0.23 g (74%); IR (KBr): $\bar{\nu}$ = 3,385, 1,655, 1,524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.98 (10H, m, $5CH_2$), 3.62 (1H, d, $^3J_{HH}$ = 4.0 Hz, OH), 3.75 (1H, m, CH), 4.96 (1H, d, $^3J_{HH}$ = 4.0 Hz, CH), 5.93 (1H, d, $^3J_{HH}$ = 7.2 Hz, NH), 7.63 (2H, d, $^3J_{HH}$ = 8.7 Hz, CH_{ar}), 7.92 (2H, d, $^3J_{HH}$ = 8.7 Hz, CH_{ar}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.65 ($2CH_2$), 25.35 (CH_2), 32.79 ($2CH_2$), 48.51 (N–CH), 73.10 (CH), 123.35 ($2CH_{ar}$), 127.96 ($2CH_{ar}$), 130.98, 131.24 ($2C_{ar}$), 169.85 (C=O) ppm.

2,6-Dichloro-N-cyclohexyl-α-hydroxybenzeneacetamide
(**3g**, $C_{14}H_{17}Cl_2NO_2$)
Viscous oil, yield 0.21 g (70%); IR (KBr): $\bar{\nu}$ = 3,400, 3,305, 1,650, 1,529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.92 (10H, m, $5CH_2$), 3.72 (1H, m, N–CH), 3.66–3.80 (1H, br s, OH), 4.96 (1H, s, CH), 5.97 (1H, d, $^3J_{HH}$ = 7.2 Hz, NH), 7.33 (3H, s, CH_{ar}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.66 ($2CH_2$), 25.39 (CH_2), 32.85 ($2CH_2$), 48.55 (N–CH), 73.10 (CH), 128.85, 129.11, 131.14, 139.98 ($6C_{ar}$), 169.78 (C=O) ppm.

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