Practical Approach for Preparation of α-Ketoamides via Direct Aminocarbonylation of Carboxylic Esters with Carbamoylsilane

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I Experimental section

II ¹H NMR data, ¹³C NMR data, IR and elemental analysis data of 3a-f, 5a-f, 7a, 7d and ¹⁹F NMR data of 7a

III ¹H NMR and ¹³C NMR spectra of 3a-f, 5a-f, 7a, 7d, 9 and ¹⁹F NMR spectrum of 7a
I Experimental section

1. General

All reactions were carried out in Schlenk tubes under a argon atmosphere. Dry toluene was freshly distilled from sodium and benzophenone as a moisture indicator under Ar atmosphere before use. Carbamoylsilane was prepared according to our previous reported methods.[21] The monitoring of reaction and checking of purity of the product were done using precoated silica gel plates (Merck TLC Silica gel 60 F254). Column chromatography was performed using silica gel 200-300 mesh. Visualization was achieved by UV (254 nm) light detection and iodine staining. 1H (600 MHz) and 13C (150.8 MHz) NMR spectra were recorded on Bruker (AV600) NMR spectrometer. All spectra were recorded at room temperature in deuterated chloroform (CDCl3) δ = 7.28 ppm (TMS: 0.019) for proton NMR, δ = 77.05 (or 77.15) ppm for carbon NMR) unless otherwise stated using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hertz (Hz). Infrared spectra were recorded as potassium bromide (KBr) discs for solids or thin films on sodium chloride plates for oils on an IMPACT–410 spectrophotometer. Elemental analysis was performed on an EA–1108 analyzer. Melting points were measured with a STUART SMP 10 melting point apparatus and uncorrected.

2. General procedure for aminocarbonylation of carboxylic esters with carbamoylsilane

A Schlenk tube fitted with a Teflon vacuum stopcock and micro stirbar was flame-heated under vacuum and refilled with Ar. Carboxylic esters (0.5 mmol) and anhydrous toluene (1.5 mL) was added at ice bath temperature. After 20 min, N,N-dimethylcarbamoylsilane 2 (0.6 mmol) was added. The sealed reaction mixture was stirred at 110 °C until no carbamoylsilane 2 could be detected by TLC. For Table 1 and Table 2, the reaction mixture was added dichloromethane (5 mL), water (2 mL) and concentrated hydrochloric acid (0.5 mL), then stirred 2 hours at room temperature, the organic layer was decanted and the aqueous phase extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over MgSO4 and evaporated to afford the crude product which was purified by column chromatography on silica gel to afford α-ketoamides 3 or 5. For Table 3, entries 1-3, the residue was directly isolated by Kugelrohr distillation to give product 7a. For Table 3, entries 4 and Scheme 2, volatiles were removed in vacuum, and the residue was chromatographed using petroleum ether–EtOAc as eluent to yield products 7d and 9.

II 1H NMR data, 13C NMR data, IR and elemental analysis data of 3a-f, 5a-f, 7a, 7d, 9 and 19F NMR data of 7a.

N,N-Dimethyl-α-oxo-4-nitrobenzeneacetamide (3a): Yellowish solid, yield 69.1% (76.8 mg, 0.5mmol), mp 137.0–138.0 °C. IR: 1698, 1650, 1512 cm⁻¹. 1H NMR: δ = 8.38–8.16 (m, 4H), 3.17 (s, 3H), 3.03 (s, 3H). 13C NMR: δ = 189.3, 165.6, 151.1, 137.5, 130.8, 124.1, 37.1, 34.3. Anal. Calcd for C10H10N2O4: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.19; H, 4.58; N, 12.55%.
**N,N-Dimethyl-α-oxo-3-nitrobenzeneacetamide (3b)**: Yellowish solid, yield 75.2% (83.5 mg, 0.5mmol), mp 119.0–120.0 °C. IR: 1698, 1654, 1532 cm⁻¹. ¹H NMR: δ = 8.78 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 7.2 Hz, 1H), 7.75 (t, J = 8.4, 7.2 Hz, 1H), 3.17 (s, 3H), 3.04 (s, 3H). ¹³C NMR: δ = 188.7, 165.5, 148.6, 135.2, 134.6, 130.3, 128.7, 124.6, 37.2, 34.4. Anal. Calc'd for C₁₀H₁₀N₂O₄: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.16; H, 4.49; N, 12.58%.

**N,N,N',N'-Tetramethyl-2-hydroxy-2-(2-nitro)phenyl malonamide (3c)**: Colorless liquid, yield 52.0% (76.8 mg, 0.5mmol). IR: 3278, 1658, 1540, 1366 cm⁻¹. ¹H NMR: δ = 7.79–7.76 (m, 1H), 7.57–7.53 (m, 2H), 7.39–7.38 (m, 1H), 6.30 (s, 1H), 3.10 (s, 6H), 2.87 (s, 6H). ¹³C NMR: δ = 169.6, 149.4, 133.0, 131.6, 129.7, 125.6, 82.0, 38.8, 38.1. Anal. Calc'd for C₁₃H₁₇N₃O₅: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.66; H, 5.85; N, 14.49%.

**N,N,N',N'-Tetramethyl-2-hydroxy-2-(2-carboxyl)phenyl malonamide (3d)**: Colorless liquid, yield 51.0% (75.1 mg, 0.5mmol). IR: 3449, 1738, 1688, 1648, 1538 cm⁻¹. ¹H NMR: δ = 7.88–7.59 (m, 4H), 5.30, 5.29 (ss, 1H), 3.02 (s, 6H), 2.99 (s, 6H). ¹³C NMR: δ = 168.9, 164.9, 146.1, 134.9, 130.3, 126.3, 125.2, 124.2, 89.3, 37.6, 37.1. Anal. Calc'd for C₁₄H₁₈N₂O₅: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.36; H, 6.35; N, 9.43%.

**N,N-Dimethyl-α-oxo-(3-methoxycarbonyl) benzeneacetamide (3e)**: Colorless liquid, yield 56.3% (66.2 mg, 0.5mmol). IR: 1737, 1698, 1649, 1311 cm⁻¹. ¹H NMR: δ = 8.58 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 3.96 (s, 3H), 3.15, 2.99 (ss, 6H). ¹³C NMR: δ = 190.6, 166.4, 165.9, 135.4, 133.6, 133.5, 131.2, 130.7, 129.3, 52.5, 37.1, 34.2. Anal. Calc'd for C₁₂H₁₃NO₄: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.47; H, 5.39; N, 5.75%.

**N,N,N',N'-Tetramethyl-2-hydroxy-2-(3-methoxycarbonyl)phenylmalonamide (3f)**: Colorless liquid, yield 70.0% (107.9 mg, 0.5mmol). IR: 3359, 1738, 1654, 1438 cm⁻¹. ¹H NMR: δ = 8.02–7.47 (m, 4H), 6.51 (s, 1H), 3.92 (s, 3H), 3.08 (s, 6H), 2.83 (s, 6H). ¹³C NMR: δ = 170.0, 169.9, 166.5, 166.4, 140.2, 140.1, 131.9, 131.8, 130.5, 130.4, 129.5, 129.4, 129.1, 128.7, 128.6, 128.3, 81.5, 81.4, 52.3, 52.2, 38.8, 38.7. Anal. Calc'd for C₁₅H₂₀N₂O₅: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.47; H, 6.38; N, 9.15%.

**N,N-Dimethyl-α-oxo-4-pyridin acetamide (5a)**: Yellowish liquid, yield 55.2% (49.2 mg, 0.5mmol). IR: 1698, 1649, 1405 cm⁻¹. ¹H NMR: δ = 8.85 (s, 2H), 8.75 (d, J = 1.8 Hz, 2H), 3.12 (s, 3H), 2.98, 2.97 (ss, 3H). ¹³C NMR: δ = 190.3, 165.4, 151.2, 139.0, 122.1, 37.0, 34.3. Anal. Calc'd for C₉H₁₀N₂O₂: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.85; H, 5.43; N, 15.52%.

**N,N-Dimethyl-α-oxo-3-pyridin acetamide (5b)**: Yellowish liquid, yield 52.3% (46.6 mg, 0.5mmol). IR: 1687, 1655, 1581 cm⁻¹. ¹H NMR: δ = 9.29 (s, 1H), 8.98 (d, J = 4.2 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.33 (t, J = 6.6 Hz, 1H), 3.16 (s, 3H), 3.07 (s, 3H). ¹³C NMR: δ = 190.1, 165.8, 154.7, 151.3, 136.8, 128.8, 123.9, 37.1, 34.3. Anal. Calc'd for C₁₀H₁₀N₂O₂: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.56; H, 5.41; N, 15.79%.

**N,N,N',N'-Tetramethyl-2-hydroxy-2-(6-fluoro-3-)pyridyl malonamide (5c)**: Yellowish solid, yield 45.2% (83.5 mg, 0.5mmol), mp 108.0–110.0 °C. IR: 3406, 1695, 1649, 1588 cm⁻¹.
$^1$H NMR: $\delta = 8.00$ (d, $J = 6.6$ Hz, 1H), 8.20 (d, $J = 7.2$ Hz, 1H), 6.94 (s, 1H), 6.00 (s br, 1H), 3.04 (s, 3H), 2.87 (s, 3H).

$^{13}$C NMR: $\delta = 169.1, 163.9, 162.3, 145.7, 145.6, 142.1, 142.0, 133.6, 133.5, 109.7, 109.4, 79.4, 38.3, 37.7$. Anal. Caled for C$_{12}$H$_{16}$FN$_3$O$_3$: C, 53.53; H, 5.99; N, 15.61.

Found: C, 53.35; H, 5.72; N, 15.51%.

N,N-Dimethyl-α-oxo-pyrazine acetamide (5d): Yellowish solid, yield 68.4% (61.3 mg, 0.5mmol), mp 96.0–98.0 °C. IR: 1689, 1649, 1399 cm$^{-1}$. $^1$H NMR: $\delta = 9.29$ (s, 1H), 8.81 (s, 1H), 8.70 (s, 1H), 3.13 (s, 3H), 2.99 (s, 3H).

$^{13}$C NMR: $\delta = 190.8, 166.6, 148.6, 146.0, 144.9, 144.3, 36.8, 34.0$. Anal. Caled for C$_8$H$_9$N$_3$O$_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.69; H, 5.28; N, 23.73%.

N,N-Dimethyl-α-oxo-2-(6-ethoxycarbonyl)pyridine acetamide (5e): Colorless solid, yield 71.3% (89.2 mg, 0.5mmol), mp 100.0–102.0 °C. IR: 1726, 1693, 1649, 1316 cm$^{-1}$. $^1$H NMR: $\delta = 8.31–8.24$ (m, 2H), 8.07–8.05 (m, 1H), 4.53–4.43 (m, 2H), 3.16 (s, 3H), 3.01 (s, 3H), 1.49–1.42 (m, 3H).

$^{13}$C NMR: $\delta = 191.3, 167.6, 164.2, 151.4, 148.7, 136.3, 128.7, 125.7, 62.0, 37.1, 33.8, 14.3$. Anal. Caled for C$_{12}$H$_{14}$N$_2$O$_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.32; H, 5.86; N, 11.38%.

N,N,N′,N′-Tetramethyl-α,α′-dioxo-2,6-pyridine diacetamide (5f): Colorless solid, yield 63.2% (87.6 mg, 0.5mmol), mp 163.0–165.0 °C. IR: 1709, 1654, 1405 cm$^{-1}$. $^1$H NMR: $\delta = 8.35–8.18$ (m, 3H), 3.12 (s, 6H), 2.94 (s, 6H).

$^{13}$C NMR: $\delta = 191.0, 167.3, 150.8, 139.2, 126.7, 36.9, 33.6$. Anal. Caled for C$_{13}$H$_{15}$N$_3$O$_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.17; H, 5.21; N, 15.30%.

N,N,N′,N′-Tetramethyl-α-hydroxy-α′-trifluoromethyl malonamide (7a): The crude product was purified by Kugelrohr distillation. Colourless solid, yield 47.0% (56.9 mg, 0.5mmol), mp 118.0–120.0 °C. IR: 3278, 1658, 1414 cm$^{-1}$. $^1$H NMR: $\delta = 5.64$ (s, 1H), 3.09 (s, 6H), 3.01 (s, 6H). $^{19}$F NMR: $\delta = -74.4$. Anal. Caled for C$_8$H$_{13}$F$_3$N$_2$O$_3$: C, 39.67; H, 5.41; N, 11.57. Found: C, 39.79; H, 5.38; N, 11.36%.

N,N-Dimethyl-α-hydroxy-α-ethoxy(trichloro)propionamide (7d): The crude product was directly purified by silica gel flash chromatography. Slightly brown liquid, yield 51.2%. (67.7 mg, 0.5 mmol). IR: 3368, 1768, 1535 cm$^{-1}$. $^1$H NMR: $\delta = 4.43–4.39$ (m, 2H), 3.21 (s, 3H), 3.07 (s, 3H), 1.62 (s, 1H), 1.42–1.36 (m, 3H). $^{13}$C NMR: $\delta = 163.6, 161.8, 79.7, 64.6, 38.5, 37.9, 13.7$. Anal. Caled for C$_7$H$_{12}$Cl$_3$NO$_3$: C, 31.81; H, 4.49; N, 5.56%.

N,N-Dimethyl-β-ethoxy-α,β-dioxo-propionamide (9): Colourless liquid, yield 67.1% (58.1 mg, 0.5 mmol). IR: 1768, 1735, 1654, 1455 cm$^{-1}$. $^1$H NMR: $\delta = 4.40$ (q, $J = 7.2$ Hz, 2H), 3.07 (s, 3H), 3.06 (s, 3H), 1.39 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR: $\delta = 180.8, 164.0, 160.5, 63.3, 36.8, 34.6, 14.0$. Anal. Caled for C$_7$H$_{11}$NO$_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.68; H, 6.60; N, 7.90%.

III $^1$H NMR and $^{13}$C NMR spectra of 3a-f, 5a-f, 7a, 7d, 9 and $^{19}$F NMR spectrum of 7a

1. $^1$H NMR spectra of 3a-f, 5a-f, 7a, 7d and 9 ($^1$H NMR (600 MHz) spectra were...
recorded on a Bruker AR600 MHz spectrometer in CDCl₃, with TMS as an internal standard.

**¹H NMR of 3a**

![NMR Spectrum of 3a]

**¹H NMR of 3b**

![NMR Spectrum of 3b]
$^1$H NMR of 3c

$^1$H NMR of 3d
$^1$H NMR of 3e

$^1$H NMR of 3f
$^1$H NMR of 5a

$^1$H NMR of 5b
$^1$H NMR of $5e$

$^1$H NMR of $5d$
$^1$H NMR of 5e

$^1$H NMR of 5f
$^1$H NMR of 7a

$^1$H NMR of 7d
1H NMR of 9

2. $^{13}$C NMR spectra of 3a-f, 5a-f, 7a, 7d, 9 and $^{19}$F NMR spectrum of 7a ($^{13}$C NMR (151 MHz) spectra were recorded on a Bruker AR600 MHz spectrometer in CDCl$_3$, with TMS as an internal standard).

$^{13}$C NMR of 3a
$^{13}$C NMR of 3d

$^{13}$C NMR of 3e
$^{13}$C NMR of 3f

$^{13}$C NMR of 5a
$^{13}$C NMR of 5f

$^{13}$C NMR of 7a
$^{13}$C NMR of 7d

$^{13}$C NMR of 9
\(^{19}\text{F NMR of 7a}\)

-74.39 ppm