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Palladium-Catalyzed Alcoholysis of 3-Iodopropynamides: Selective Synthesis of Carbamoylacetates

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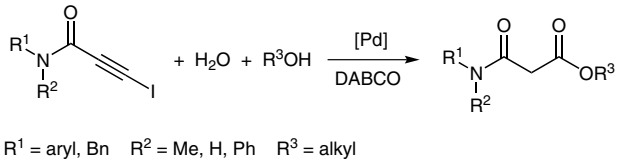

R^1 = aryl, Bn R^2 = Me, H, Ph R^3 = alkyl

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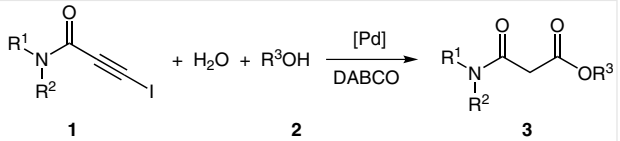
Abstract A novel and selective method for the synthesis of carbamoylacetates via the alcoholysis of 3-iodopropynamides has been developed. 3-Iodopropynamides react with alcohols in the presence of palladium(II) acetate and DABCO to afford the corresponding carbamoylacetates in moderate to good yields.

Key words palladium, 1,4-diazabicyclo[2.2.2]octane, alcoholysis, 3-iodopropynamides, carbamoylacetates

Carbamoylacetates are versatile synthetic building blocks that are used for the synthesis of many natural products and related compounds of biological and medicinal importance.[1] The traditional synthetic approach to carbamoylacetates is direct condensation of anilines with monoethyl malonates or alkyl malonyl chlorides. A few alternative methods, such as palladium-catalyzed carbonylation of diazo compounds with carbon monoxide,[2] palladium/light-catalyzed carbonylation of α-iodoacetates, carbon monoxide, and amines,[3] and other reactions,[4] have been reported. Alkynyl iodides are a class of important compounds that have been used widely in organic synthesis.[5] Recently, we also reported a modified protocol for the synthesis of internal alkynes, such as *N*,3-diarylpropynamides, by the palladium(II) acetate catalyzed Suzuki–Miyaura cross-coupling reaction of alkynyl iodides with arylboronic acids.[5f] Interestingly, however, in a similar reaction using 1,4-diazabicyclo[2.2.2]octane (DABCO) as base, we found that the envisioned internal alkyne was obtained only in low yield, and the carbamoylacetate was formed as the principal product. This led us to investigate the alcoholysis reaction, and here we present an efficient palladium and DABCO system catalyzed alcoholysis of 3-iodopropynamides to carbamoylacetates under an air atmosphere (Scheme 1).

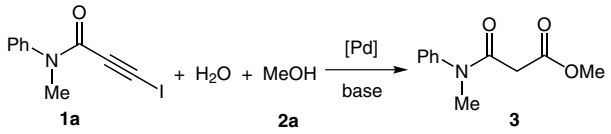


R^1 = aryl, Bn R^2 = Me, H, Ph R^3 = alkyl

Scheme 1 Palladium-catalyzed synthesis of carbamoylacetates

The reaction between 3-iodo-*N*-methyl-*N*-phenylpropynamide (**1a**) and methanol (**2a**) was chosen as a model reaction to screen the optimal reaction conditions; the results are summarized in Table 1. Initially, the effects of varying the palladium catalyst were examined. The results showed that treatment of **1a** with **2a** using 2.0 mol% palladium catalyst and two equivalents of DABCO in acetonitrile under an air atmosphere for 12 hours afforded the desired product **3** in 52, 71, 62, and 83% yields, respectively (entries 1–4). Palladium(II) acetate was the best catalyst in terms of yield, and the amount of palladium(II) acetate also affected the yield to some extent (entries 4–7). A variety of other bases, such as triethylamine, 4-(dimethylamino)pyridine, potassium *tert*-butoxide, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were then investigated, and they were inferior to DABCO (entries 4 and 8–11). It was noted that the reaction does not take place with cesium carbonate (entry 12). Finally, the use of various solvents, including methanol, tetrahydrofuran, *N*,*N*-dimethylformamide, 1,2-dichloroethane, and toluene, was also examined, and acetonitrile provided the highest yield (entries 4 and 13–17); methanol gave identical results to acetonitrile (entry 13). In view of the high-boiling or complex alcohols which were not easily purified, acetonitrile was chosen over methanol as a solvent.

Table 1 Screening Optimal Conditions[a]



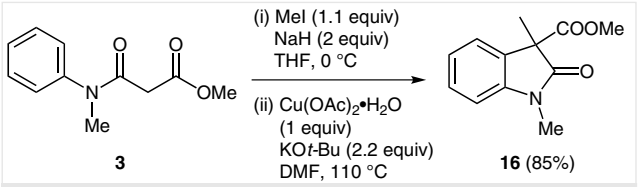
1a **2a** **3**

Entry	Palladium catalyst (mol%)	Base	Solvent	Isolated yield (%)
1	$Pd(dba)_2$ (2.0)	DABCO	MeCN	52
2	$PdCl_2$ (2.0)	DABCO	MeCN	71
3	$PdCl_2(PPh_3)_2$ (2.0)	DABCO	MeCN	62
4	$Pd(OAc)_2$ (2.0)	DABCO	MeCN	83
5	$Pd(OAc)_2$ (1.0)	DABCO	MeCN	76
6	$Pd(OAc)_2$ (0.5)	DABCO	MeCN	55
7	$Pd(OAc)_2$ (5.0)	DABCO	MeCN	83
8	$Pd(OAc)_2$ (2.0)	Et_3N	MeCN	48
9	$Pd(OAc)_2$ (2.0)	DMAP	MeCN	15
10	$Pd(OAc)_2$ (2.0)	KO*t*-Bu	MeCN	30
11	$Pd(OAc)_2$ (2.0)	DBU	MeCN	22
12	$Pd(OAc)_2$ (2.0)	Cs_2CO_3	MeCN	0
13	$Pd(OAc)_2$ (2.0)	DABCO	MeOH	83
14	$Pd(OAc)_2$ (2.0)	DABCO	THF	27
15	$Pd(OAc)_2$ (2.0)	DABCO	DMF	25
16	$Pd(OAc)_2$ (2.0)	DABCO	DCE	11
17	$Pd(OAc)_2$ (2.0)	DABCO	toluene	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), base (2 equiv), solvent (2 mL), r.t., 12 h, air atmosphere.

With the optimal reaction conditions in hand, the scope of the 3-iodopropynamide and alcohol was investigated (Table 2). Initially, we turned our attention to examine suitable alcohols for the reaction. The results demonstrated that a variety of alcohols **2b**–**e** all worked well with 3-iodo-*N*-methyl-*N*-phenylpropynamide (**1a**) in moderate to good yields (entries 1–4). For example, reaction of **2b** or **2c** with **1a** in the presence of 2.0 mol% palladium catalyst and two equivalents of DABCO in acetonitrile under an air atmosphere for 12 hours gave the corresponding carbamoylacetates **4** and **5** in 83 and 75% yields, respectively (entries 1 and 2). The addition of benzyl alcohol afforded the product **6** in good yield (entry 3). Gratifyingly, the sterically hindered tertiary alcohol **2e** was also consistent with the reaction conditions, and gave the desired product **7** in moderate yield (entry 4). Subsequently, a number of 3-iodopropynamides **1b**–**h** were examined in the presence of the alcohol, palladium(II) acetate, and DABCO (entries 5–11). We found that reaction of substituted phenyl 3-iodopropynamides **1b** and **1c** with ethanol (**2b**) afforded the corresponding products **8** and **9** in 81 and 78% yields, respectively (entries 5 and 6). Comparing *N*-phenyl- with *N*-(*o*-tolyl)- and *N*-(*m*-tolyl)propynamides, *meta* substitution on the phenyl ring was found to have some effect on the reaction, and the yield of **12** slightly decreased to 60% compared to 71–73% for **10** and **11** (entries 7–9). Although the activity was reduced for the reaction, 3-iodo-*N*,*N*-diphenylpropynamide (**1g**) and *N*-benzyl-3-iodo-*N*-methylpropynamide (**1h**) were also suitable substrates leading to the desired products **13** and **14** smoothly in moderate yields (entries 10 and 11). Surprisingly, the reaction of phenyl 3-iodopropynoate (**1i**) with ethanol (**2b**) afforded the ester-exchanged product, diethyl malonate (**15**), in 42% yield (entry 12). However, no product was generated using 3-iodo-*N*-methyl-*N*-phenylpropynamide (**1a**) and diethylamine (**2f**) under the optimal reaction conditions.

The products of alcoholysis of 3-iodopropynamides provide an attractive and useful route to introduce new groups in the synthesis of natural products. For example, methyl 3-[methyl(phenyl)amino]-3-oxopropanoate (**3**) underwent a methylation–cyclization route to give an oxoindoline derivative **16** in good yield (Scheme 2).[6]



3 **16** (85%)

Scheme 2 Application of carbamoylacetates

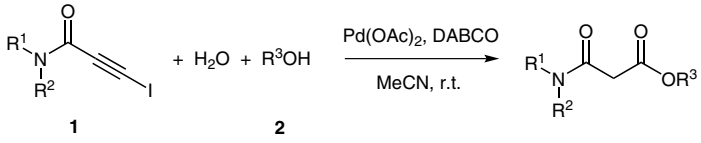
In summary, we have developed a novel, efficient and facile protocol for the synthesis of carbamoylacetates by the palladium(II) acetate/DABCO system catalyzed alcoholysis of 3-iodopropynamides under aerobic conditions. This protocol is simple and highly general for the diverse substrate scope, which provides a valuable complement to traditional methods. Further utilization of this procedure will continue in our laboratory.

Chemicals were purchased from commercial supplier (Aldrich, USA, and Changsha Chemical Company, China) and used without purification prior to use. NMR spectroscopy was performed on a Bruker-500 spectrometer operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). TMS was used an internal standard and $CDCl_3$ was used as the solvent. HRMS data were performed on a micro-TOF mass spectrometer.

3-Iodo-*N*-methyl-*N*-phenylpropynamide (1a); Typical Procedure

To a solution of propynoic acid (154.0 mg, 2.2 mmol) and *N*-methylaniline (214.0 mg, 2 mmol) in CH_2Cl_2 (6 mL) was added gradually a solution of DCC (453.2 mg, 2.2 mmol) in CH_2Cl_2 (6 mL) at 0 °C, then the mixture was stirred at r.t. for 1 h. After purification, the product was then treated with NIS (495 mg, 2.2 mmol) and $AgNO_3$ (34.0 mg, 0.2 mmol) in acetone at r.t. under an air atmosphere for 8 h until complete consumption of the starting material (TLC and GC analysis).[7] When the reaction was finished, sat. $Na_2S_2O_3$(10 mL) was added to the mixture, and then aqueous phase was extracted with Et_2O. The combined organic extracts were dried (anhyd Na_2SO_4), and evaporated in

Table 2 Alcoholysis of 3-Iodopropynamide **1**[a]



1 **2**

Entry	Propynamide	R^1	R^2	Alcohol	R^3	Product	Yield[b] (%)
1	**1a**	Ph	Me	**2b**	Et	**4**	83
2	**1a**	Ph	Me	**2c**	$CH_2CH{=}CH_2$	**5**	75
3	**1a**	Ph	Me	**2d**	Bn	**6**	80
4	**1a**	Ph	Me	**2e**	*t*-Bu	**7**	66
5	**1b**	4-MeC_6H_4	Me	**2b**	Et	**8**	81
6	**1c**	4-ClC_6H_4	Me	**2b**	Et	**9**	78
7	**1d**	Ph	H	**2a**	Me	**10**	71
8	**1e**	2-MeC_6H_4	H	**2a**	Me	**11**	73
9	**1f**	3-MeC_6H_4	H	**2a**	Me	**12**	60
10	**1g**	Ph	Ph	**2a**	Me	**13**	55
11	**1h**	Bn	Me	**2a**	Me	**14**	48
12[c]	**1i**	–[d]	–[d]	**2b**	Et	**15**	42
13	**1a**	Ph	Me	**2f**	–[e]	–[f]	–[f]

[a] Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), DABCO (2 equiv), MeCN (2 mL), r.t., air atmosphere, 12 h.
[b] Isolated yield.
[c] Diethyl malonate (**15**) was obtained.
[d] Substrate was phenyl 3-iodopropynoate.
[e] Diethylamine was used.
[f] No reaction.

vacuo, the residue was purified by flash column chromatography (silica gel, hexane–EtOAc) to give the corresponding 3-iodo-*N*-methyl-*N*-phenylpropynamide (**1a**).

Substrates **1** were synthesized according to the typical procedure. Substrates **1a**,**b**,**d**,**g**,**i** are known; **1c**,**e**,**f**,**h**, with structures similar to the known compounds, were confirmed by GC-MS and used directly for the alcoholysis reaction.

***N*-(4-Chlorophenyl)-3-iodo-*N*-methylpropiolamide (1c)**

MS (EI, 70 eV): *m*/*z* (%) = 319 (64) $[M]^+$, 291 (6), 262 (32), 140 (100), 111 (40).

3-Iodo-*N*-(2-tolyl)propiolamide (1e)

MS (EI, 70 eV): *m*/*z* (%) = 285 (80) $[M]^+$, 257 (18), 179 (100), 158 (55), 130 (76).

3-Iodo-*N*-(3-tolyl)propiolamide (1f)

MS (EI, 70 eV): *m*/*z* (%) = 285 (76) $[M]^+$, 257 (16), 179 (100), 158 (60), 130 (72).

***N*-Benzyl-3-iodo-*N*-methylpropiolamide (1h)**

MS (EI, 70 eV): *m*/*z* (%) = 299 (85) $[M]^+$, 271 (18), 242 (28), 120 (100).

Carbamoylacetates 3–15; General Procedure

A mixture of 3-iodopropynamide **1** (0.2 mmol), alcohol **2** (0.4 mmol), $Pd(OAc)_2$ (0.896 mg, 0.004 mmol), and DABCO (44.8 mg, 0.4 mmol) was stirred in MeCN (2 mL) at r.t. for 12 h until complete consumption of the starting material (TLC and GC analysis). When the reaction was complete, sat. $Na_2S_2O_3$ (10 ml) was added to the mixture and it was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (anhyd Na_2SO_4) and evaporated in vacuo and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane) to afford the desired product (Table 2).

Methyl 3-[Methyl(phenyl)amino]-3-oxopropanoate (3)[1e]

Colorless oil; yield: 34.4 mg (83%).

IR (KBr): 1747, 1651 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2 H), 7.38 (d, *J* = 7.0 Hz, 1 H), 7.24–7.23 (m, 2 H), 3.68 (s, 3 H), 3.31 (s, 3 H), 3.23 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.1, 165.9, 143.4, 129.9, 128.3, 127.2, 52.2, 41.3, 37.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}NO_3$: 207.0895; found: 207.0889.

Ethyl 3-[Methyl(phenyl)amino]-3-oxopropanoate (4)[1e]

Slightly yellow oil; yield: 36.7 mg (83%).

IR (KBr): 1740, 1666 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (t, *J* = 7.5 Hz, 2 H), 7.37 (d, *J* = 7.0 Hz, 1 H), 7.24 (d, *J* = 7.5 Hz, 2 H), 4.15–4.11 (m, 2 H), 3.31 (s, 3 H), 3.21 (s, 2 H), 1.25 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 166.1, 143.5, 130.0, 128.3, 127.3, 61.3, 41.6, 37.5, 14.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1048.

Allyl 3-[Methyl(phenyl)amino]-3-oxopropanoate (5)[1e]

Pale yellow oil; yield: 35.0 mg (75%).

IR (KBr): 1744, 1667 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (t, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 9.0 Hz, 1 H), 7.25 (t, *J* = 10.5 Hz, 2 H), 5.92–5.83 (m, 1 H), 5.32–5.21 (m, 2 H), 4.57 (d, *J* = 7.0 Hz, 2 H), 3.31 (s, 3 H), 3.25 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.4, 165.9, 143.5, 131.7, 130.0, 128.3, 127.3, 118.6, 65.8, 41.5, 37.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1047.

Benzyl 3-[Methyl(phenyl)amino]-3-oxopropanoate (6)[1f]

Colorless oil; yield: 45.3 mg (80%).

IR (KBr): 1746, 1660 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 8 H), 7.20–7.17 (m, 2 H), 5.12 (s, 2 H), 3.31 (s, 3 H), 3.27 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6, 165.8, 143.4, 135.5, 130.0, 128.5, 128.4, 128.3, 128.3, 127.2, 67.0, 41.6, 37.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{17}NO_3$: 283.1208; found: 283.1202.

***tert*-Butyl 3-[Methyl(phenyl)amino]-3-oxopropanoate (7)**[1e]

Colorless oil; yield: 32.9 mg (66%).

IR (KBr): 1735, 1664 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 2 H), 7.37 (d, *J* = 7.0 Hz, 1 H), 7.23 (t, *J* = 6.5 Hz, 2 H), 3.30 (s, 3 H), 3.18 (s, 2 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 166.4, 143.7, 129.8, 128.1, 127.3, 81.5, 42.7, 37.4, 28.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{19}NO_3$: 249.1365; found: 249.1359.

Ethyl 3-[Methyl(*p*-tolyl)amino]-3-oxopropanoate (8)[1d]

Colorless oil; yield: 38.1 mg (81%).

IR (KBr): 1741, 1667 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 12.0 Hz, 2 H), 7.11 (d, *J* = 5.5 Hz, 2 H), 4.15–4.10 (m, 2 H), 3.28 (s, 3 H), 3.21 (s, 2 H), 2.38 (s, 3 H), 1.23 (t, *J* = 8.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 166.2, 141.0, 138.2, 130.5, 127.0, 61.2, 41.5, 37.4, 21.1, 14.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1203.

Ethyl 3-[4-Chlorophenyl(methyl)amino]-3-oxopropanoate (9)[1d]

White solid; yield: 39.8 mg (78%); mp 49–50 °C.

IR (KBr): 1741, 1666 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 10.5 Hz, 2 H), 7.19 (d, *J* = 10.5 Hz, 2 H), 4.16–4.10 (m, 2 H), 3.29 (s, 3 H), 3.20 (s, 2 H), 1.24 (t, *J* = 9.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 166.2, 142.0, 134.1, 130.1, 128.7, 61.3, 41.4, 37.4, 14.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{14}ClNO_3$: 255.0662; found: 255.0658.

Methyl 3-Oxo-3-(phenylamino)propanoate(10)[4a]

Brown solid; yield: 27.4 mg (71%); mp 42–44 °C.

IR (KBr): 1740, 1670 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.29 (t, *J* = 8.0 Hz, 2 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 3.75 (s, 3 H), 3.46 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 163.3, 137.4, 128.8, 124.5, 120.0, 52.4, 41.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}NO_3$: 193.0739; found: 193.0734.

Methyl 3-Oxo-3-(*o*-tolylamino)propanoate (11)[8]

Colorless oil; yield: 30.2 mg (73%).

IR (KBr): 1741, 1668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.22–7.19 (m, 2 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 3.82 (s, 3 H), 3.53 (s, 2 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 162.8, 135.6, 130.4, 128.5, 126.7, 125.0, 122.2, 52.6, 41.0, 17.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}NO_3$: 207.0895; found: 207.0889.

Methyl 3-Oxo-3-(*m*-tolylamino)propanoate (12)[9]

Pale yellow solid; yield: 24.8 mg (60%); mp 38–40 °C.

IR (KBr): 1742, 1666 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.10 (s, 1 H), 7.38 (s, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 6.94 (d, *J* = 7.0 Hz, 1 H), 3.79 (s, 3 H), 3.47 (s, 2 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 162.8, 138.9, 137.3, 128.8, 125.4, 120.7, 117.2, 52.6, 41.5, 21.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}NO_3$: 207.0895; found: 207.0888.

Methyl 3-(Diphenylamino)-3-oxopropanoate (13)[10]

White solid; yield: 29.6 mg (55%); mp 81–83 °C.

IR (KBr): 1734, 1649 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 10 H), 3.67 (s, 3 H), 3.41 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 165.8, 129.9, 128.9, 128.5, 128.3, 126.3, 126.2, 52.3, 42.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{15}NO_3$: 269.1052; found: 269.1047.

Methyl 3-[Benzyl(methyl)amino]-3-oxopropanoate (14)[1b]

Brown oil; yield: 21.2 mg (48%).

IR (KBr): 1745, 1699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 2 H), 7.29–7.27 (m, 3 H), 4.62 (s, 2 H), 3.77 (s, 3 H), 3.54 (s, 2 H), 2.92 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 166.4, 136.7, 128.7, 127.9, 126.4, 52.5, 50.9, 41.3, 35.3.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1046.

Diethyl Malonate (15)[11]

Colorless oil; yield: 13.4 mg (42%).

IR (KBr): 1747, 1733 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.22–4.18 (m, 4 H), 3.37 (s, 2 H), 1.30–1.27 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 61.2, 41.4, 13.8.

MS (EI, 70 eV): *m*/*z* (%) = 160 (2) $[M]^+$, 133 (67), 115 (100).

Methyl 1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate (16); Typical Procedure

To a solution of methyl 3-[methyl(phenyl)amino]-3-oxopropanoate (**3**, 103.5 mg, 0.5 mmol) and NaH (24 mg, 1 mmol) in THF (4 mL) was added gradually MeI (78.1 mg, 0.55 mmol) at 0 °C, then the mixture was stirred for 5 min to afford methyl 2-methyl-3-[methyl(phenyl)amino]-3-oxopropanoate. After purification, the product was used for the cyclization reaction.

A mixture of methyl 2-methyl-3-[methyl(phenyl)amino]-3-oxopropanoate (44.2 mg, 0.2 mmol), $Cu(OAc)_2·H_2O$ (39.9 mg, 0.2 mmol), and KO*t*-Bu (49.3 mg, 0.44 mmol) in DMF (3 mL) was stirred at 110 °C for 1 h. Then sat. NH_4Cl solution (10 mL) was added to the mixture and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (anhyd Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc) to afford the desired product (**16**)[6] (37.2 mg, 85%) as a white solid; mp 83–85 °C.

IR (KBr): 1743, 1611 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (t, *J* = 7.5 Hz, 1 H), 7.27–7.26 (m, 1 H), 7.08 (t, *J* = 6.5 Hz, 1 H), 6.87 (d, *J* = 6.5 Hz, 1 H), 3.68 (s, 3 H), 3.28 (s, 3 H), 1.70 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 170.3, 143.6, 130.3, 129.1, 123.1, 122.9, 108.5, 54.9, 53.0, 26.6, 20.2.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{13}NO_3$: 219.0895; found: 219.0891.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379104.

References

(1) For reviews, see: (a) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934. (b) Adediran, S. A.; Cabaret, D.; Lohier, J.-F.; Wakselman, M.; Pratt, R. F. *Bioorg. Med. Chem.* **2010**, *18*, 282. (c) Russo, A.; Galdi, G.; Croce, G.; Lattanzia, A. *Chem. Eur. J.* **2012**, *18*, 6152. (d) Wang, J.; Yuan, Y.; Xiong, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 2210. (e) Ghosh, S.; De, S.; Kakde, B. N.; Bhunia, S.; Adhikary, A.; Bisai, A. *Org. Lett.* **2012**, *14*, 5864. (f) Bhunia, S.; Ghosh, S.; Dey, D.; Bisai, A. *Org. Lett.* **2013**, *15*, 2426.

(2) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330.

(3) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Synlett* **2012**, *23*, 1331.

(4) (a) Graziano, M. L.; Cimminiello, G. *Synthesis* **1989**, 54. (b) López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *Tetrahedron Lett.* **2001**, *42*, 4479. (c) Tuba, R.; Ungváry, F. *J. Mol. Catal. A: Chem.* **2003**, *203*, 59. (d) Balogh, J.; Kégl, T.; Ungváry, F.; Skoda-Földes, R. *Tetrahedron Lett.* **2009**, *50*, 4727.

(5) For reviews, see: (a) Yan, J.; Li, J. H.; Cheng, D. P. *Synlett* **2007**, 2442. (b) Rajender Reddy, K.; Venkateshwar, M.; Uma Maheswari, C.; Santhosh Kumar, P. *Tetrahedron Lett.* **2010**, *51*, 2170. (c) Usanov, D. L.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 1286. (d) Chen, D. X.; Cao, Y.; Yuan, Z. L.; Cai, H. T.; Zheng, R. W.; Kong, L. C.; Zhu, G. G. *J. Org. Chem.* **2011**, *76*, 4071. (e) Li, Y. B.; Liu, X. H.; Jiang, H. F.; Liu, B. F.; Chen, Z. W.; Zhou, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 6341. (f) Tang, J. S.; Xiang, X. Y.; Wang, Z. J.; Li, J. H. *Synthesis* **2011**, 2789. (g) Tang, J. S.; Tian, M.; Sheng, W. B.; Guo, C. C. *Synthesis* **2012**, *44*, 540. (h) Zeng, W.; Wu, W. Q.; Jiang, H. F.; Sun, Y. D.; Chen, Z. W. *Tetrahedron Lett.* **2013**, *54*, 4605.

(6) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249.

(7) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755.

(8) Mahboobi, S.; Eichhorn, E.; Winkler, M.; Sellmer, A.; Moellmann, U. *Eur. J. Med. Chem.* **2008**, *43*, 633.

(9) Chakraborty, K.; Devakumar, C. *J. Agric. Food Chem.* **2006**, *54*, 6800.

(10) Manikowski, A.; Kolarska, Z. *Synth. Commun.* **2009**, *39*, 3621.

(11) Kuang, Y.; Liu, X.; Chang, L.; Wang, M.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 3814.

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