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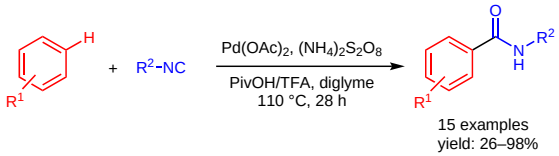
Synthesis of Benzamide Derivatives by the Reaction of Arenes and Isocyanides through a C–H Bond Activation Strategy

Mehdi Khalaj *[a]
Mahboubeh Taherkhani[b]
Seyed Mahmoud Mousavi-Safavi[a]
Jafar Akbari[a]

[a] Young Researchers and Elite Club, Buinzahra Branch, Islamic Azad University, Buinzahra, Iran
[b] Young Researchers and Elite Club, Takestan Branch, Islamic Azad University, Takestan, Iran
khalaj_mehdi@yahoo.com



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Abstract A carbon–carbon bond formation reaction between isocyanides and benzene derivatives is reported. In contrast to traditional cross-coupling reactions, which require aryl halides or pseudohalides, we use a palladium catalyst to generate the aryl–palladium through C–H bond activation of arenes. This method offers an attractive approach to a range of benzamides from readily accessible benzene derivatives.

Keywords C–H bond activation, palladium salt, benzamide, isocyanide

C–H bond activation enables the conversion of readily available starting materials into valuable functionalized organic compounds and the efficient structural editing of already complex compounds.[1–6] While the selective transformation of ubiquitous but inert C–H bonds into other functional groups is a long-standing challenge (due to a high bond dissociation energy and very low polarity),[7] palladium-catalyzed reactions have recently offered tremendous advances due to the unique reactivity of palladium. For example, Fujiwara reported a pioneering activation of aromatic C–H bonds for the addition to C–C multiple bonds.[8] Yu et al. have developed an outstanding *meta*-C–H activation/olefination process for electronic-deficient arenes catalyzed by palladium salts.[9] Substantial progress towards palladium (II)-catalyzed arene–arene coupling has been made by Lu et al.[10] Liu reported a palladium-catalyzed cross-coupling of aromatic compounds with carboxylic acids through C–H bond activation.[11] Kozlowski reported the first chemoselective activation of sp^3 versus sp^2 C–H bonds with Pd (II) in the absence of a directing group.[12] Zhang reported a pioneering benzylic C–H bond activation to form benzylic ester derivatives with $Pd(OAc)_2$ catalysis under O_2.[13] Fagnou has reported a catalytic C–H activation/functionalization of unactivated arenes with indoles to form 3-aryl substituted indoles.[14]

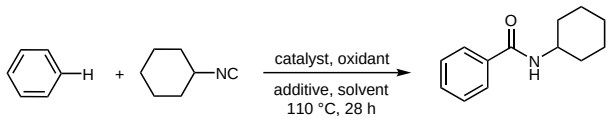
In this respect, it becomes clear that the introduction of a new functionality directly through C–H bond activation unlocks opportunities for markedly different synthetic strategies and leads to the formation of complex products from simpler starting materials. However, using this strategy for the direct amidocarboxylation of aromatic compounds is a challenging goal. Alkyl and aryl isocyanides have been utilized both as the carbonyl and amine source to form amide derivatives by using metal-catalyzed cross-coupling reactions.[15–19] Of course, the use of cheap and readily available arenes as the source of aryls instead of substrates such as aryl halides, aryl diazonium salts, or carboxylic acids makes this procedure very attractive from economical and environmental points of view. These findings encouraged us to examine a C–H bond activation strategy to form benzamide derivatives in a reaction involving isocyanides and unactivated arenes.

Our investigation began with coupling of benzene (**1a**) with cyclohexyl isocyanide (**2a**) using $Pd(OAc)_2$ as the catalyst and $K_2S_2O_8$ as an oxidant at 120 °C. Selected results from our screening experiments are summarized in Table 1. Stirring in DCE for 28 hours in the absence of an additive only produced trace quantities of the desired product (Table 1, entry 1). The addition of H_2O as an additive completely inhibited the reaction and *p*-toluenesulfonic acid (TsOH), trifluoroacetic acid (TFA), and trifluoromethanesulfonic acid (TfOH) were also ineffective (Table 1, entries 2–5). Gratifyingly, a significant increase in yield occurred using pivalic acid (PivOH) (Table 1, entry 6). As such, PivOH may play an important role that goes beyond completing the catalytic cycle including the adjustment of steric effects on the catalyst species. Optimization of the reaction conditions demonstrated that the reaction was most productive when

using diglyme as the solvent, while the reaction conducted in dioxane or MeCN led to lower conversions (Table 1, entries 7–9). As anticipated, amidocarboxylation was not observed when the substrates were heated in the absence of a palladium salt or an oxidizing agent (not shown in Table 1). After a series of oxidants had been examined, $(NH_4)_2S_2O_8$ was found to be the most effective, giving **3a** in 52% yield (Table 1, entry 7). Oxone, Ag_2O, $Cu(OAc)_2$, and *tert*-butyl hydroperoxide (TBHP) were unsuitable for this transformation (Table 1, entries 10–13), and $Ce(SO_4)_2$ was also ineffective (Table 1, entry 14). When the reaction was performed with use of iodosobenzene or trifluoroacetic anhydride $(TFA)_2O$ as an oxidizing agent[20,21] **3a** was isolated in 75 and 63% yield, respectively (Table 1, entries 15 and 16). However, $(NH_4)_2S_2O_8$ was selected as the oxidant of choice on the basis of a balance of cost and efficiency. The effect of the palladium salt on the reaction outcome was also considered and it was found that $Pd(OAc)_2$ gave a higher yield of the product compared with other commercially available palladium salts (Table 1, entries 17–19). It is worth mentioning that the reduction of the amount of the catalyst, oxidant, and **2a** resulted in formation of the product in lower yields (not shown in Table 1), whereas a significant increase in yield occurred when the reaction was conducted with PivOH and TFA (Table 1, entry 20).

After having defined the optimum reaction conditions (Table 1, entry 7), we sought to explore the scope of the reaction (Table 2). We found that isocyanide derivatives could be successfully converted into the corresponding benzamides in acceptable yields within a range of substrates. Amidocarboxylation of benzene (**1a**) proceeded with acceptable yields using cyclohexyl and cyclopentyl isocyanide (**2a** and **2b**) (Table 2, entries 1 and 2). *iso*-Propyl isocyanide (**2c**) gave the product in moderate yield (Table 2, entry 3). The reactions conducted with bulky isocyanides **2d** and **2e** resulted in good yields (Table 2, entries 4 and 5). The reaction conducted with benzyl isocyanide (**2f**) gave the desired product in moderate yield (Table 2, entry 6). *N*-phenyl

Table 1 Optimization of Reaction Conditions[a]



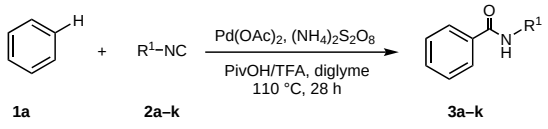
1a **2a** **3a**

Entry	Catalyst	Oxidant	Additive	Solvent	Yield (%)
1	$Pd(OAc)_2$	$K_2S_2O_8$	–	DCE	traces
2	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	H_2O	DCE	–
3	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	TsOH	DCE	traces
4	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	TFA	DCE	13
5	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	TfOH	DCE	traces
6	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	PivOH	DCE	37
7	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	PivOH	diglyme	52
8	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	PivOH	dioxane	traces
9	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	PivOH	MeCN	traces
10	$Pd(OAc)_2$	Oxone	PivOH	diglyme	–
11	$Pd(OAc)_2$	Ag_2O	PivOH	diglyme	14
12	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	diglyme	11
13	$Pd(OAc)_2$	TBHP	PivOH	diglyme	–
14	$Pd(OAc)_2$	$Ce(SO_4)_2$	PivOH	diglyme	–
15	$Pd(OAc)_2$	PhIO	PivOH	diglyme	51
16	$Pd(OAc)_2$	TFAA	PivOH	diglyme	46
17	$Pd(MeCN)_2Cl_2$	$(NH_4)_2S_2O_8$	PivOH	diglyme	14
18	$PdCl_2$	$(NH_4)_2S_2O_8$	PivOH	diglyme	traces
19	$Pd(acac)_2$	$(NH_4)_2S_2O_8$	PivOH	diglyme	26
20	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	PivOH/ TFA	diglyme	70[b]

[a] Reaction conditions: **1a** (5.0 mmol), **2a** (1.0 mmol), Pd salt (10 mol%), oxidant (1.5 mmol), additive (1.2 mmol), solvent (2.0 mL), 110 °C for 28 h.
[b] Reaction conducted with PivOH (0.5 mmol) and TFA (1.0 mL) as additive system.

and -naphthyl benzamide (**3g** and **3h**) were also obtained in good yields (Table 2, entries 7–8). Somewhat surprisingly, this reaction is not sensitive to steric effects, as 2,6-dimethylphenyl isocyanide (**2i**) afforded the desired product in good yields (Table 2, entry 9). It is worth mentioning that electron-rich aryl isocyanide **2j** gave the corresponding product in excellent yield (Table 2, entry 10). We also found that the reaction of *tert*-butyl isocyanoacetate (**2k**) proceeded very well to afford the corresponding amide in good yield (Table 2, entry 11).

Table 2 Reaction Scope for Isocyanides[a]

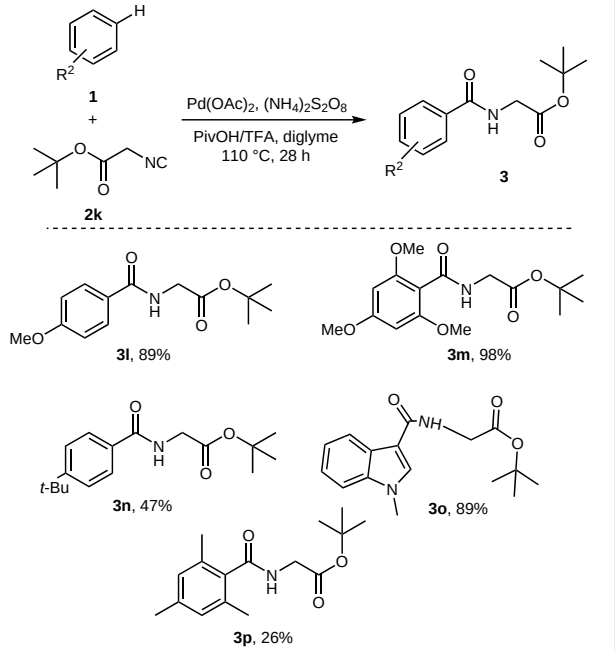


Entry	2	R^1	Yield (%)	M.p. (°C)[b]
1	**a**	cyclohexyl	**3a**, 70	155–157
2	**b**	cyclopentyl	**3b**, 72	159–161
3	**c**	*i*-Pr	**3c**, 59	97–99
4	**d**	*t*-Bu	**3d**, 75	137–139
5	**e**	1,1,3,3-tetramethylbutyl	**3e**, 73	73–75
6	**f**	Bn	**3f**, 56	106–108
7	**g**	Ph	**3g**, 83	162–164
8	**h**	2-naphtyl	**3h**, 81	186–189
9	**i**	2,6-dimethylphenyl	**3i**, 78	163–165
10	**j**	4-methoxyphenyl	**3j**, 91	157–158
11	**k**	*t*-BuOCOCH$_2$	**3k**, 80	–

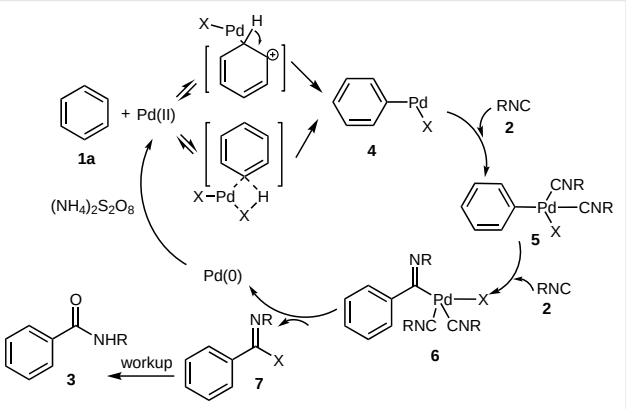
[a] Reaction conditions: **1a** (5.0 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $(NH_4)_2S_2O_8$ (1.5 mmol), PivOH (0.5 mmol), TFA (1.0 mL), diglyme (2.0 mL), 110 °C for 28 h.
[b] Melting point.

The transformation was further generalized, allowing the coupling of a range of benzene derivatives (Scheme 1). Electron-rich arenes afforded the corresponding products **3l** and **3m** in good yields. Contrarily, product **3n**, containing a bulky *tert*-butyl group, was achieved in low yield. *N*-Methyl indole was converted into the desired product **3o** smoothly in good yield, whereas mesitylene also afforded the corresponding product **3p** in low yield.

Insufficient data exist at present to allow a detailed mechanistic discussion. The facile formation of **4** through electrophilic metalation of the aromatic C–H bond has been reported previously.[8,22,23] A possible mechanism could involve the formation of intermediate **4**, either through an electrophilic aromatic metalation pathway or by concerted proton transfer metalation,[14] followed by coordination of isocyanide to form **5**.[24] Then, intermediate **6** can be formed by migratory insertion of isocyanide into **6**.[16] A subsequent reductive elimination of intermediate **6** will form the Pd(0) species and intermediate **7** which is further transformed into the desired product **3** upon acidic workup. The Pd(0) species is reoxidized to the Pd(II) species by the action of $(NH_4)_2S_2O_8$ to complete the catalytic cycle (Scheme 2).[25]



Scheme 1 Reaction scope of arenes; reaction conditions: **1a** (5.0 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $(NH_4)_2S_2O_8$ (1.5 mmol), PivOH (0.5 mmol), TFA (1.0 mL), diglyme (2.0 mL), 110 °C for 28 h



Scheme 2 Possible reaction pathway

In conclusion, we have introduced a new catalytic system for the direct amidocarboxylation of arenes with isocyanides.[26] A range of isocyanides has been coupled to simple arenes in moderate to good yields. While a significant advance, the transformation suffers from the limitations of requiring excess arenes and a low structural diversity of the arenes used. Further studies are being conducted to improve the reaction scope.

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(26) **Typical procedure for the preparation of 3**

$Pd(OAc)_2$ (10 mol%), PivOH (0.5 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol), arene (5.0 mmol), TFA (1.0 mL), and diglyme (3.0 mL) were added to a test tube. The mixture was then evacuated and flushed with argon (3 times) and stirred for 30 min at 25 °C. Afterwards, the isocyanide (1.0 mmol) was added by microsyringe. The reaction mixture was then stirred at 110 °C for 28 h and then allowed to cool to room temperature. The crude reaction mixture was diluted with H_2O (10 mL) and stirred for 30 min, followed by addition of EtOAc (5 mL) and a saturated $NaHCO_3$ solution (3 mL). The mixture was stirred for an additional 30 min and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc 3:1) to give the desired product.

The spectroscopic data of all known compounds were satisfactory and consistent with those reported in the literature.[16–18]

***tert*-Butyl benzoylglycinate (3k)**

White solid. M.p.: 72–74 °C. Yield: 0.19 g (80%). IR (KBr) (ν_{max}, cm^{-1}): 3245, 3073, 2928, 1734, 1649, 1538, 1332, 1152. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.67 (s, 9 H, 3 CH_3), 4.32 (d, ^3J = 6.1 Hz, 2 H, CH_2), 7.55–7.61 (m, 3 H, 3 CH), 7.97 (d, ^3J = 6.6 Hz, 2 H, 2 CH), 8.35 (br d, ^3J = 6.1 Hz, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.1 (3 CH_3), 46.9 (CH_2), 87.0 (C), 128.9 (2 CH), 129.6 (2 CH), 131.8 (CH), 136.5 (C), 165.1 (CH), 167.3 (C) ppm. MS: *m/z* (%) = 235 ($[M]^+$, 5), 175 (39), 105 (100), 77 (68), 57 (87). Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.70; H, 7.42; N, 6.13.

***tert*-Butyl (4-methoxybenzoyl)glycinate (3l)**

Colorless solid. M.p.: 96–98 °C. Yield: 0.24 g (89%). IR (KBr) (ν_{max}, cm^{-1}): 3355, 3034, 2979, 1731, 1635, 1312, 1176. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.63 (s, 9 H, 3 CH_3), 3.79 (s, 3 H, OCH_3), 4.26 (d, ^3J = 6.3 Hz, 2 H, CH_2), 7.06 (d, ^3J = 6.8 Hz, 2 H, 2 CH), 7.79 (d, ^3J = 6.8 Hz, 2 H, 2 CH), 8.49 (br d, ^3J = 6.3 Hz, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 34.2 (3 CH_3), 46.1 (CH_2), 57.0 (OCH_3), 85.1 (C), 117.1 (2 CH), 128.2 (C), 130.1 (2 CH), 162.1 (C), 165.6 (CH), 168.0 (C) ppm. MS: *m/z* (%) = 265 ($[M]^+$, 4), 208 (31), 135 (100), 107 (63), 74 (53), 57 (81). Anal. Calcd for $C_{14}H_{19}NO_4$ (265.31): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.61; H, 7.39; N, 5.49.

***tert*-Butyl (2,4,6-trimethoxybenzoyl)glycinate (3m)**

Pale yellow solid. M.p.: 156–158 °C. Yield: 0.32 g (98%). IR (KBr) (ν_{max}, cm^{-1}): 3245, 3073, 2928, 1733, 1653, 1538, 1332, 1152. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.57 (s, 9 H, 3 CH_3), 3.78 (s, 3 H, OCH_3), 3.83 (s, 6 H, 2 OCH_3), 4.24 (d, ^3J = 5.8 Hz, 2 H, CH_2), 6.36 (s, 2 H, 2 CH), 8.28 (br d, ^3J = 5.8 Hz, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 33.1 (3 CH_3), 46.4 (CH_2), 56.2 (OCH_3), 57.4 (2 OCH_3), 83.6 (C), 97.8 (2 CH), 118.6 (C), 158.9 (2 C), 161.5 (C), 165.0 (CH), 167.6 (C) ppm. MS: *m/z* (%) = 325 ($[M]^+$, 13), 268 (24), 195 (100), 167 (65), 131 (56), 57 (87). Anal. Calcd for $C_{16}H_{23}NO_6$ (325.36): C, 59.07; H, 7.11; N, 4.31. Found: C, 59.28; H, 7.25; N, 4.44.

***tert*-Butyl (4-(*tert*-butyl)benzoyl)glycinate (3n)**

Colorless solid. M.p.: 89–91 °C. Yield: 0.14 g (47%). IR (KBr) (ν_{max}, cm^{-1}): 3265, 3070, 2967, 1736, 1638, 1544, 1329, 1144. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.29 (s, 9 H, 3 CH_3), 1.60 (s, 9 H, 3 CH_3), 4.47 (d, ^3J = 6.4 Hz, 2 H, CH_2), 7.38 (d, ^3J = 6.9 Hz, 2 H, 2 CH), 7.79 (d, ^3J = 6.9 Hz, 2 H, 2 CH), 8.32 (br d, ^3J = 6.4 Hz, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 30.4 (3 CH_3), 33.8 (3 CH_3), 39.1 (C), 46.9 (CH_2), 85.1 (C), 128.1 (2 CH), 128.6 (2 CH), 134.3 (C), 153.2 (C), 165.3 (CH), 167.9 (C) ppm. MS: *m/z* (%) = 291 ($[M]^+$, 1), 234 (27), 161 (85), 133 (29), 130 (46), 57 (100). Anal. Calcd for $C_{17}H_{25}NO_3$ (291.39): C, 70.07; H, 8.65; N, 4.81. Found: C, 70.29; H, 8.92; N, 4.98.

***tert*-Butyl (1-methyl-1H-indole-3-carbonyl)glycinate (3o)**

Yellow solid. M.p.: 97–99 °C. Yield: 0.26 g (89%). IR (KBr) (ν_{max}, cm^{-1}): 3231, 3065, 2979, 1739, 1643, 1547, 1344, 1124. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.56 (s, 9 H, 3 CH_3), 3.51 (s, 3 H, CH_3), 4.10 (d, ^3J = 6.0 Hz, 2 H, CH_2), 7.52–7.60 (m, 3 H, 3 CH), 8.22 (br d, ^3J = 6.0 Hz, 1 H, NH), 8.28 (s, 1 H, CH), 8.40 (d, ^3J = 6.9 Hz, 1 H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 33.1 (3 CH_3), 36.9 (CH_3), 45.7 (CH_2), 83.8 (C), 114.1 (CH), 114.6 (C), 123.1 (CH), 123.4 (CH), 125.8 (CH), 128.2 (C), 134.5 (CH), 138.0 (C), 165.7 (CH), 168.2 (C). MS: *m/z* (%) = 288 ($[M]^+$, 7), 273 (16), 231 (28), 158 (89), 131 (52), 57 (100) ppm. Anal. Calcd for $C_{16}H_{20}N_2O_3$ (288.35): C, 66.65; H, 6.99; N, 9.72. Found: C, 66.83; H, 7.24; N, 9.89.

***tert*-Butyl (2,4,6-trimethylbenzoyl)glycinate (3p)**

Pale yellow solid. M.p.: 107–109 °C. Yield: 0.07 g (26%). IR (KBr) (ν_{max}, cm^{-1}): 3240, 3043, 2978, 1740, 1641, 1530, 1344, 1141.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.61 (s, 9 H, 3 CH_3), 2.32 (s, 3 H, CH_3), 2.38 (s, 6 H, 2 CH_3), 4.37 (d, ^3J = 5.6 Hz, 2 H, CH_2), 6.91 (s, 2 H, 2 CH), 8.31 (br d, ^3J = 5.6 Hz, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 20.7 (2 CH_3), 24.1 (CH_3), 33.5 (3 CH_3), 47.0 (CH_2), 83.1 (C), 129.6 (2 CH), 132.3 (2 C), 136.1 (C), 143.8 (C), 165.2 (CH), 167.9 (C) ppm. MS: *m/z* (%) = 277 ([M]$^+$, 3), 220 (32), 147 (67), 131 (58), 119 (81), 57 (100). Anal. Calcd for $C_{16}H_{23}NO_3$ (277.36): C, 69.29; H, 8.36; N, 5.05. Found: C, 69.53; H, 8.61; N, 5.24.