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Facile synthesis of 2-benzoxazoles *via* CuI/2,2′-bipyridine catalyzed intramolecular C–O coupling of 2-haloanilides

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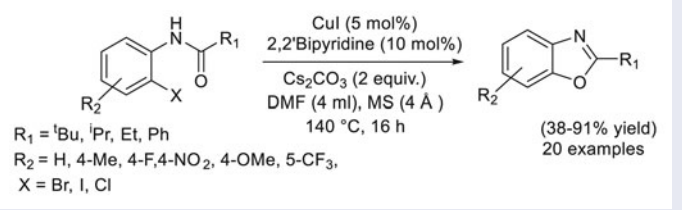
ABSTRACT

Development of newer methods for the synthesis of Benzoxazoles has of greater interest due to their wide range of biological activities and pharmaceutical importance. We herein report a facile and general method for the synthesis of 2-substituted Benzoxazoles *via* copper catalyzed intramolecular C–O cross-coupling of 2-haloanilides. A combination of CuI (5 mol%), 2,2′-bipyridine (10 mol%), Cs_2CO_3 (2 equiv.) in DMF solvent with 4 Å molecular sieves at 140 °C, illustrated the scope for tuning the reactivity of 2-haloanilides toward the selective formation of a series of 2-alkyl benzoxazole derivatives in moderate to good yields. This is the first systematic study using CuI/2,2′-Bipyridine as the catalytic system for the synthesis of 2-substituted Benzoxazoles. The outcome of the reaction was found to be significantly influenced by the aromatic and amide substituents of 2-haloanilides.

GRAPHICAL ABSTRACT



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Benzoxazole; copper; 2-haloanilides; 2,2′-bipyridine; C–O coupling

Introduction

Benzoxazole derivatives are privileged heterocyclic organic compounds which are present in a large number of natural products and are particularly significant due to their promising medicinal activities (Figure 1).[1] This class of heterocyclic molecules forms skeletal part of various therapeutically useful compounds such as HIV reverse transcriptase inhibitor,[2] DNA topoisomerase II inhibitor,[3] estrogen β-receptor agonists ERB-041,[4] selective peroxisome proliferator-activated receptor γ antagonistJTP-426467,[5] Cathespin S inhibitor,[6] anticancer agent NSC 693838,[7] anti-microbial agent[8] and antitumor agent.[9] Benzoxazole moieties are also found application as

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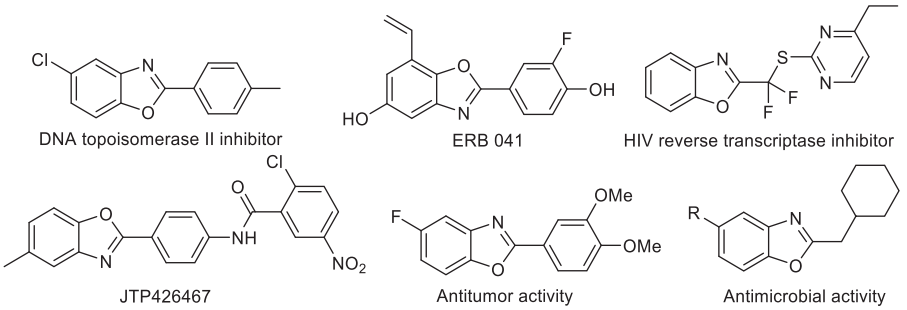


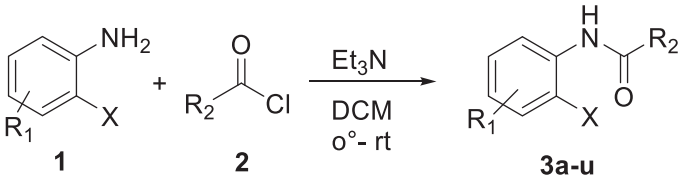
Figure 1. Some biologically active 2-benzoxazole derivatives.

important scaffold in fluorescent probes.[10] In last few decades, tremendous effort has been devoted for developing synthetic procedures for 2-substituted benzoxazoles preparation. The classical method for the synthesis of benzoxazole involves the condensation of *o*-aminophenol with potential acyl sources such as aldehydes,[11] carboxylic acid,[12] acyl halides,[13] esters,[14] benzylic alcohol,[15] nitriles,[16] benzylic amine,[17] alkynes,[18] 1,1-dibromo alkenes[19] or 1,3-diketone[20] under oxidative reaction conditions. These methods often suffer from some drawbacks such as harsh reaction conditions and the limited availability of suitably substituted starting materials within a multistep pathway.

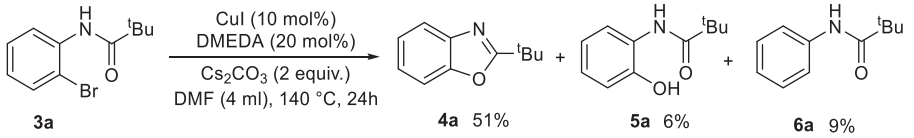
Recently, some of these drawbacks have been overcome by the development of transition metal catalyzed intramolecular C–O coupling of 2-haloanilides leading to benzoxazole derivatives under milder reaction conditions[21] Transition metal catalyzed intramolecular oxidative C–H functionalization of a number of substrates is also explored for the construction of 2-substituted benzoxazoles.[22] Most of these reactions are performed under homogenous conditions and the ligands chelated with the metals play a crucial role in the catalysis. Among these, copper-catalyzed reactions have attracted considerable attention due to its cost-effectiveness and easy availability. These methods usually adopt a straightforward route with wide substrate scope for the synthesis of these target heterocycle *via* intramolecular *O*-arylation of N-(2-halophenyl)-benzamides using suitable chelating ligands.[23] Although significant improvements have been achieved for the synthesis of 2-aryl benzoxazoles, the efforts to develop a general and efficient catalytic system for the synthesis of 2-alkyl substituted benzoxazoles is still demanding.[24] In addition, earlier studies for the synthesis of 2-alkyl benzoxazoles exposed that, the selection of suitable ligand is very crucial for obtaining high yields. The present work describes a facile and general method for the synthesis of a number of 2-alkyl benzoxazoles using inexpensive and easily available CuI/2,2'-bipyridine as catalytic system. To the best of our knowledge, there is no systematic study available, using CuI/2,2'-bipyridine system targeting the synthesis of 2-substituted benzoxazoles from 2-haloanilides.

Results and discussion

2-Haloanilide precursors (**3a–u**) used in this study was synthesized from corresponding 2-halo anilines (**1**) and acid chlorides (**2**) following the literature procedure (Scheme 1).[25,27] We commenced our C–O coupling studies with N-(2-bromophenyl) pivalamide **3a**



Scheme 1. Synthesis of 2-haloanilides.



Scheme 2. Copper catalyzed reaction of 2-haloanilide.

as model substrate. The reaction of **3a** with CuI (10 mol%) and DMEDA (20 mol%) in presence of Cs_2CO_3 base in DMF at 140 °C for 24 h, resulted in the formation of 2-*tert*-butyl benzoxazole **4a** in 51% isolated yield along with 6%*o*-hydroxylated product **5a** and 9% debrominated product **6a** (Scheme 2).Similar formation of *o*-hydroxylated product and debrominated product from corresponding 2-haloanilides with CuO nanoparticles in water were observed earlier by Patel and coworkers and interestingly, under their reaction condition, none of the *o*-halophenyl alkylamides provided 2-alkyl benzoxazoles.[26] These observations prompted us to carry out detailed optimization studies to identify a suitable reaction condition towards the selective formation of 2-alkyl benzoxazole.

Subsequently, a series of experiments were carried out using **3a** to optimize the reaction condition and the results are tabulated in Tables 1 and 2. Our initial efforts started with the screening of various ligands under the standard reaction condition as described in Scheme 1. Reactions with 1,10-Phenanthroline as the ligand resulted in the formation of **4a** in 69% isolated yield along with 3% and 6% of **5a** and **6a** respectively (Table 1, entry 2). PPh_3 found to be less effective ligand for the desired coupling reaction and comparable amount of the debrominated product **6a** was also formed (Table 1, entry 3). The use of DABCO and 8-hydroxy quinolone afforded the benzoxazole **4a** in 53% and 60% respectively (Table 1, entries 4 and 5). Lower yields and poor selectivity for the formation of **4a** were observed, in the case of *L*-Proline and Pyridine ligands (entries 6 and 7, Table 1). Sterically bulky and electron donating 2,2'-bipyridyl ligands were also studied and provided moderate yields of **4a** along with smaller amounts of **5a** and **6a** (Table 1, entries 8–10). To our delight, when 2,2-bipyridine was chosen, the yield of **4a** was increased to 76%, along with3% of **5a** and 4% of **6a** (Table 1, entry 11). Therefore,2,2'-bipyridine was selected as the optimal ligand for further catalyst screening studies using various copper catalysts. However, none of the copper salts such as CuOAc, CuBr, $Cu(OAc)_2$, $CuBr_2$ or $CuCl_2$ gave better yield and selectivity than CuI (entries 12–16). Notably, when the reaction in entry 11 was repeated using lower stoichiometric amounts of the copper catalyst (5 mol%) and 2,2'-bipyridine ligand (10 mol%), nearly same yields of **4a** and **5a** were isolated and only trace amount of **6a** was detected in GC (Table 1, entry 17). More interestingly, highly selective formation of **4a** was achieved in better yield (80%) in 16 hours by the addition of molecular sieves (4 Å) in the reaction medium (Table 1, entry 18). In this case, the formation of the

Table 1. Ligand Screening studies of **3a** under copper catalysis.[a]

Entry	Catalayt (Cu)	Ligand(L)	[d]Yield of **4a**/**5a**/**6a** (%)
1	CuI	DMEDA	51/6/9
2	CuI	1,10-phenanthroline	69/3/6
3	CuI	PPh_3	17/3/14
4	CuI	DABCO	53/2/8
5	CuI	8-Hydroxy quinoline	60/5/6
6	CuI	*L*-Proline	34/3/13
7	CuI	Pyridine	36/6/9
8	CuI	4,4′-di-t-butyl-2,2′-bipyridyl	54/7/8
9	CuI	5,5′-dimethyl-2,2′-bipyridyl	57/5/6
10	CuI	4,4′-dimethyl-2,2′-bipyridyl	56/4/6
11	CuI	2,2′-Bipyridine	76/3/4
12	Cu(OAc)	2,2′-Bipyridine	59/4/7
13	CuBr	2,2′-Bipyridine	61/6/8
14	$CuCl_2$	2,2′-Bipyridine	54/8/10
15	$Cu(OAc)_2$	2,2′-Bipyridine	59/12/8
16	$CuBr_2$	2,2′-Bipyridine	61/11/8
17[b]	CuI	2,2′-Bipyridine	75/3/trace
18[b,c]	**CuI**	**2,2′-Bipyridine**	**80/0/trace**

Reaction conditions:
[a]Cu (10 mol%), L (20 mol%), Cs_2CO_3 (2 equiv.), DMF (4 ml), 140 °C, 24 h.
[b]CuI (5 mol%), L (10 mol%) is used. Only trace of **6a** observed in GC.
[c]Carried out in presence of 4 Å Molecular sieves for 16 h, trace of **6a** observed in GC.
dIsolated yields.

Table 2. CuI/2,2′-Bipyridine catalyzed reaction of **3a** with various bases and solvents.

Entry	Base	Solvent	Temp	[a]Yield (%) of **4a**
1	Cs_2CO_3	DMF	140	80
2	K_3PO_4	DMF	140	66
3	Na_2CO_3	DMF	140	26
4	K_2CO_3	DMF	140	28
5	$KHCO_3$	DMF	140	26
6	Cs_2CO_3	DMSO	140	26
7	Cs_2CO_3	1,4-Dioxane	100	20
8	Cs_2CO_3	CH_3CN	80	0
9	Cs_2CO_3	Toluene	110	0
10	Cs_2CO_3	DCE	100	42
11	Cs_2CO_3	DMF	100	30

Reaction conditions: CuI (5 mol%), 2,2′-Bipyridine (10 mol%), Base (2 equiv.), Solvent (4 ml), MS (4 Å), 140 °C, 16 h.
aIsolated yields.

hydroxylated product **5a** was completely prevented and only trace amount of the debrominated product **6a** was detected in GC.

Inspired from the initial results, we continued our optimization studies with **2a** by varying reaction parameters such as base, solvent, temperature (Table 2). No other base as effective as cesium carbonate was observed. The use of K_3PO_4 base afforded only in 66% of the benzoxazole formation (Table 2, entry 2,), while the use of bases like Na_2CO_3, K_2CO_3, $KHCO_3$ in DMF solvent at 140 °C, resulted in the drastic decrease the reaction yields (Table 2, entries 3–5,). A brief survey of various solvents revealed that DMF is the best solvent for promoting this reaction in an effective manner. The reactions in solvents such as DMSO, 1,4-dioxane and DCE gave poorer results (Table 2, entries 6, 7, and 10), whereas the reaction did not work at all in acetonitrile and toluene (Table 2, entry 8 and 9) when conducted at their boiling points. Attempts to lower the reaction temperature (Table 2, entry 11) led to a significant decrease in the isolated yield (30%), hence, we decided to proceed with DMF at 140 °C.

Table 3. Control experiments using **3a**.[a]

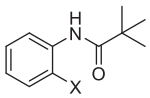
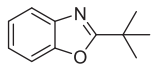
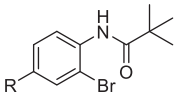
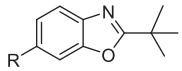
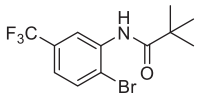
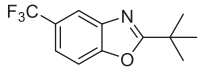
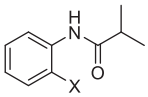
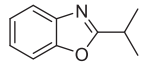
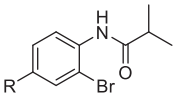
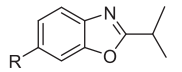
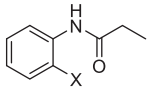
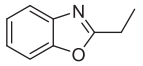
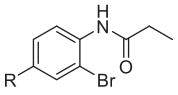
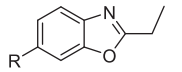
Entry	Catalyst	Ligand	base	(%) Yield of **4a**
1	CuI	2,2′-Bipyridine	–	0
2	–	2,2′-Bipyridine	Cs_2CO_3	0
3	CuI	–	Cs_2CO_3	38
4[b]	CuI	2,2′-Bipyridine	Cs_2CO_3	25[c]

[a]Reaction conditions: CuI (5 mol%), 2,2′-Bipyridine (10 mol%), Cs_2CO_3 (2 equiv.), DMF (4 ml), MS (4 Å), 140 °C, 16 h.
[b]reaction carried in DMF/H_2O (1:1).
[c]**5a** was also isolated in **43**% yield along with 5% of **6a**.

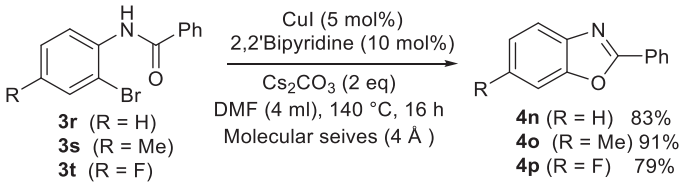
To understand the role of catalyst, ligand, base, and solvent in this reaction, a set of control experiments were carried out (Table 3) and found that without catalyst (Table 3, entry 1) or base (Table 3, entry 2), the reaction will not work. However, when the reaction was performed without ligand only 38% of **4a** was obtained (Table 3, entry 3). These results clearly confirm the indispensable role of catalyst and base in the cyclization of 2-haloanilides and the need of a suitable ligand to provide better yields. Moreover, when this reaction was carried out in presence of water (Table 3, entry 4), hydoxylated product **5a** was isolated as major product (43%), along with 25% of **4a** and 5% of **6a**. This result together with the previous observation (entry18, Table 1), clearly discloses that the presence of moisture in the reaction medium significantly affects the outcome of the reaction and favors *ortho*-hydroxylation over intramolecular C–O coupling reaction under these reaction conditions. Therefore, based on the results of optimization studies and control experiments, CuI (5 mol%), 2,2'-bipyridine (10 mol%), Cs_2CO_3 (2 equiv.) in DMF (with 4 Å MS) at 140 °C was selected as the optimized condition for the synthesis of various 2-alkyl benzoxazoles from corresponding 2-haloanilides.

With the optimized reaction conditions in hand, we have extended the scope of this intramolecular *O*-arylation strategy over broad range of 2-haloanilides and the results are summarized in Table 4. The effects of different substituents on both the aryl as well as amide moiety on 2-haloanilides were tested under the standard reaction conditions. 2-Iodoanilide **3b** displayed the similar reactivity to give the product **4a** in slightly lower yield (Table 4, entry 2), while 2-Chloroanilide **3c** was found to be less reactive (47% yield) compared to their bromo-analogue (Table 4, entry 3). The generality studies revealed that the reaction yields are significantly influenced by the nature of the aromatic substituents, especially in the *para* position of 2-haloanilides. When electron donating 4-Methoxy and 4-Methyl groups are present, corresponding benzoxazoles are formed in higher yields (Table 4, entries 4 and 7). The substrate **3e** with 4-F substituent afforded corresponding benzoxazole **4c** in 75% yield (entry 5, Table 4). However, 2-haloanilides **3f** and **3h** having electron withdrawing groups such as CF_3 and NO_2 on the *para* position of amide moiety remain unreactive and failed to produce benzoxazole products (Table 4, entry 6 and 8). However, 2-haloanilides with 5-CF_3 substitution (**3i**) reacted to give the corresponding C–O coupled product **4g** in moderate yield (Table 4, entry 9). It is also observed that the alkyl substituents at the amide group of 2-halo anilides also influencing the cyclization pathway and exhibited the reactivity in the order *tert*-butyl > isopropyl > ethyl, under the reaction condition. The isobutyramide derivatives **3j–3m**, and propionamide derivatives **3n–3q**, successfully underwent the cyclization reaction to give the corresponding benzoxazoles respectively (Table 4, entries

Table 4. Results of the generality studies.

Entry	Substrate	Product	Yield (%)
1	 **3a** X=Br	 **4a**	80
2	**3b** X=I		77
3	**3c** X=Cl		47
4	 **3d** R=Me	 **4b**	84
5	**3e** R=F		**4c**	75
6	**3f** R=CF_3		**4d**	0
7	**3g** R=OMe		**4e**	86
8	**3h** R=NO_2		**4f**	0
9	 **3i**	 **4g**	52
10	 **3j** X=Br	 **4h**	71
11	**3k** X=I		47
12	 **3l** R=Me	 **4i**	63
13	**3m** R=F		**4j**	46
14	 **3n** X=Br	 **4k**	51
15	**3o** X=I		38
16	 **3p** R = Me	 **4l**	58
17	**3q** R = F		**4m**	43

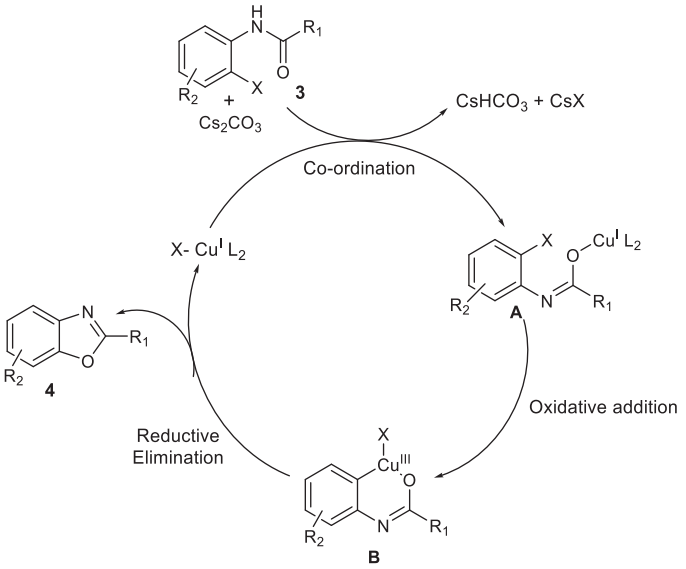
Reaction conditions: CuI (5 mol%), 2,2'-Bipyridine (10 mol%), Cs_2CO_3 (2 eq.), DMF (4 ml, with 4 Å MS), 140 °C, 16 h



Scheme 3. Copper/2,2′-Bipyridene catalyzed synthesis of 2-phenyl Benzoxazoles.

10–17). In these cases, it was also noted that the products **4h–4j** and **4k–4m** were isolated in lower amounts than corresponding pivalamide derivatives. We have also investigated the scope of extending this protocol towards the synthesis of various 2-phenyl benzoxazoles (Scheme 3). N-(2-bromophenyl) benzamides with 4-H (**3r**), 4-Me (**3s**) and 4-F (**3t**) substituents efficiently reacted to furnish the phenyl benzoxazoles **4n, 4o** and **4p** in 83%, 91%, and 79% yields respectively.

A tentative mechanism involving the catalytic cycle for the formation of benzoxazole derivatives through intramolecular cyclization of 2-haloanilides is illustrated in Scheme 4. First step involves the formation of complex **A** *via* coordination of the 2-haloanilide **3** with the active catalyst in presence of the base. Then the complex **A** undergoes intramolecular oxidative addition to C–X bond leading to the intermediate **B,** which on reductive



Scheme 4. Plausible mechanism of the reaction.

elimination would afford the desired benzoxazole product **4** along with the concomitant release of the active catalyst.

Conclusion

In conclusion, we have developed a facile and general strategy for the selective and efficient synthesis of 2-alkyl benzoxazoles from 2-haloanilides under CuI/2,2'-bipyridine catalytic system. This is the first systematic study using CuI/2,2'-bipyridine system targeting the synthesis of 2-substituted benzoxazoles from *2*-haloanilides. A variety of 2-haloanilides showed good compatibility and afforded moderate to good yields of corresponding 2-alkyl benzoxazole under the optimized reaction condition. This study also revealed that the outcome of the reaction significantly depended on the reaction conditions and the electronic demand of the substituents of 2-haloanilides, which is in agreement with the proposed mechanism. All the synthesized compounds are characterized by means of ^{1}H NMR, 13C NMR, FT-IR, and HRMS analyses and these compounds can serve as potential intermediates or scaffolds for the synthesis of various biologically and medicinally relevant compounds.

Experimental

General

All Chemicals and solvents were purchased from commercial suppliers and the solvents were distilled at their boiling point ranges prior to use. All reactions were carried under air atmosphere in oven-dried glassware. Reactions were monitored by thin layer chromatography using silica gel 60 F_{254} plates (Merck) and were visualized by fluorescence quenching under UV light. Compounds were isolated and purified by Column

chromatography with silica gel (60–120 mesh) using a mixture of ethyl acetate and hexane as eluent. ^{1}H and 13C NMR (400 MHz and 100 MHz respectively) spectra were recorded on a Bruker nuclear resonance spectrometer using $CDCl_3$ as the solvent and chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00). In assignment of the NMR spectra, multiplicities and abbreviations used are as follows: Ar = Aromatic, Ph = Phenyl, s = singlet d = doublet, t = triplet, q = quartet, dd = doublet of doublets and m = multiplet. Infrared spectra (IR) were measured on a Shimadzu ATR-FTIR spectrometer and HRMS analyses were conducted on Xevo G2 Q ToF (water) mass spectrometer

Synthesis of 2-tert-butyl benzoxazole (4a)

To a dried sealed tube, 2-haloanilide (**3a)** (0.6 mmol), CuI (0.03 mmol), 2,2'-bipyridine (0.06 mmol), Cs_2CO_3 (2 equiv.) were added followed by DMF (4 ml) and 4 Å molecular sieves (0.1g).The reaction mixture was then stirred at 140 °C for 16 h under air atmosphere and the progress of the reaction was monitored by TLC. On completion of the reaction, the reaction mixture was diluted with ethyl acetate, filtered through celite pad. The diluted solution was then extracted with ethyl acetate (10 × 3 ml) and brine solution. The organic layer was separated and dried over anhydrous Na_2SO_4, and concentrated under vacuum. The resulting crude product (**4a**) was purified by column chromatography on silica gel using n-hexane/ethyl acetate as eluent to afford the pure product. The same procedure was adopted for rest of the compounds (**4b–4p**)

Data for **4a**: Colourless oil. Yield: 80%. R_f = 0.46 (Hexane/EtOAc =95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.60 (m, 1H), 7.40–7.38 (m, 1H), 7.20–7.18 (m, 2H), 1.41 (s, 9H). 13C NMR (100 MHz, $CDCl_3$): δ 173.5, 150.8, 141.2, 124.4, 123.9, 119.7, 110.3, 34.1, 28.5. IR (neat): 2970, 2918, 1610, 1564, 1456, 1244, 1126, 1099, 750 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{11}H_{14}NO$: 175.0997; found: 176.1088 ($M + H^+$)

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