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Palladium-catalyzed cycloaminocarbonylation of 2-aminomethyl- and 2-alkylcarbamoylaryl tosylates with CO

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ABSTRACT

The palladium-catalyzed cycloaminocarbonylation of 2-(aminomethyl)aryl tosylates with CO has been established, by which a variety of salicylaldehyde derived 2-(aminomethyl)aryl tosylates may be cyclocarbonylated in the presence of CO, to afford the corresponding substituted isoindolinones in moderate to excellent yields. Furthermore, the method is also effective for the synthesis of isoindoline-1,3-diones and 2-alkyl-1*H*-benzo[*e*]isoindol-3(2*H*)-ones from 2-(*N*-alkylcarbamoyl)aryl tosylates and 1-(aminomethyl)-naphthalene-2-yl tosylates, respectively.

Introduction

Substituted isoindolinones are important structural components of a vast array of naturally occurring and pharmacologically active molecules. For example, currently many drugs, such as indoprofen (antiinflammatory),[1] lactonamycin (antibacterial),[2] and hericenone B (platelet aggregation inhibitory),[3] hold such types of heterocycles as their core structure. Furthermore, such types of heterocycles are also valuable intermediates[4] in organic synthesis. The importance of these lactam derivatives justifies a long-standing interest in the development of efficient and versatile approaches to their synthesis and new isoindolinone-based structures for the fine-tuning of their biological or physical properties for final application.

Transition metal-catalyzed carbonylative coupling reactions have become a powerful tool in organic synthesis.[5–7] A particularly attractive route to the formation of the isoindolinone core is based on cycloaminocarbonylation of suitable preformed or in situ generated *o*-halobenzylamine precursors, which can allow the regioselective preparation of the final heterocycles with the desired substitution pattern. The synthesis of isoindolinone derivatives via palladium-catalyzed cycloaminocarbonylation of *o*-halobenzyl amines was first described by Ban and co-workers in 1978 (Scheme 1, path a).[8] The cycloaminocarbonylation of 2-bromobenzaldehyde with primary amines under CO pressure leading to isoindolinones was later developed by Cho and Ren (Scheme 1, path b).[9] The use of 2-iodobenzyl bromide has also been investigated in cycloaminocarbonylation (Scheme 1, path c).[10] Orito and co-workers developed an elegant approach for the synthesis of isoindolinones by direct cyclocarbonylation of aromatic C–H bonds with CO in benzylamines using a $Pd(OAc)_2/Cu(OAc)_2$/air system in toluene solution at 120 °C (Scheme 1, path d),[11] but further studies are required, in particular with regard to the regiochemistry of the reactions when meta-substituted aniline derivatives are employed.

2-(Aminomethyl)aryl tosylates are attractive alternatives to conventional *o*-halobenzylamines due to their easy synthesis from cheap salicylal precursors by routine synthetic reactions.[12] In addition, 2-(aminomethyl)aryl tosylates are typically cheaper and lower toxic than the corresponding aryl halides. Aryl arenesulfonates have been a difficult class of substrates toward transition-metal-catalyzed C–C bond formation.[13] Among these transformations, a few examples of alkoxycarbonylation[12,14] and aminocarbonylation[14a,15] of aryl sulfonates have been reported. Despite significant recent advances in this area, aminocarbonylation of aryl tosylates remains a significant challenge. In the most aminocarbonylative cases attempts to switch from aryl perfluoroalkanesulfonate substrates to the corresponding tosylates were unsuccessful even under more forceful conditions.[15a] To the best of our knowledge, no method has been established for the catalytic transformation of aryl

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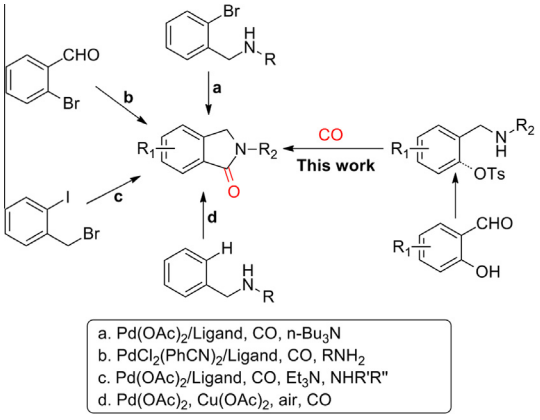


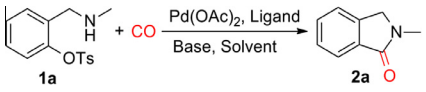
Scheme 1. Comparison of the prior cycloaminocarbonylative works to the current work.

tosylates to the corresponding benzolactams. Herein, we describe our results on the development of a practical process for the cycloaminocarbonylation of 2-(aminomethyl)aryl tosylates.

Results and discussion

Our initial screening of reaction conditions focused on the cycloaminocarbonylation of 2-(*N*-methylaminomethyl)aryl tosylate (**1a**) with CO in the presence of $Pd(OAc)_2$ (Table 1). We elected to employ $Pd(OAc)_2$ as the catalyst, as $Pd(OAc)_2$ has provided good results in aminocarbonylation of aryl and vinyl sulfonates. Influence of various factors such as ligands, solvents, and bases on the reaction was examined. In a series of preliminary screening of ligands (Table 1, entries 1–6), it was found that 1,3-bis(diphenyphosphino)propane (dppp), seem to be ideal for the cycloaminocarbonylation, whereas $P(tBu)_3{\cdot}HBF_4$, Xantphos, $PCy_3{\cdot}HBF_4$, 1,3-bis(diphenyphosphino)ethane (dppe), and 1,3-bis(diphenyphosphino)butane (dppb) tend to shut down the reacting system. Shortening the reaction time was adverse to the reaction (Table 1, entry 7). Among the solvents screened, CH_3CN gave the most promising results. In general, the use of organic bases (e.g., Et_3N) provides the desired **2a** in low yield, and other inorganic bases, such as Cs_2CO_3 and Na_2CO_3, were also less effective (Table 1, entries 10–12). The ratio of reagents, particularly substrate/Pd/dppp, was found to be important for the reaction (Table 1, entries 13–17). In addition, reducing the reaction temperature to 120 °C would lead to a dramatically lowered yield (Table 1, entry 18).

Table 1
Ligand, Solvent, and Base Effects[a]



Entry	Solvent	Ligand (mol %)	Base (equiv)	Yield[b] (%)
1	CH_3CN	$P(^tBu)_3{\cdot}HBF_4$ (10)	K_2CO_3 (2.0)	Trace
2	CH_3CN	Xantphos (10)	K_2CO_3 (2.0)	Trace
3	CH_3CN	$PCy_3{\cdot}HBF_4$ (10)	K_2CO_3 (2.0)	Trace
4	CH_3CN	dppe (10)	K_2CO_3 (2.0)	10
5	CH_3CN	dppb (10)	K_2CO_3 (2.0)	Trace
6	CH_3CN	dppp (10)	K_2CO_3 (2.0)	60
7[c]	CH_3CN	dppp (10)	K_2CO_3 (2.0)	33
8[d]	CH_3CN	dppp (10)	K_2CO_3 (2.0)	59
9	DMAc	dppp (10)	K_2CO_3 (2.0)	6
10	CH_3CN	dppp (10)	Cs_2CO_3 (2.0)	13
11	CH_3CN	dppp (10)	Na_2CO_3 (2.0)	32
12	CH_3CN	dppp (10)	NEt_3 (2.0)	30
13[e]	CH_3CN	dppp (10)	K_2CO_3 (2.0)	38
14	CH_3CN	dppp (15)	K_2CO_3 (2.0)	89
15	CH_3CN	dppp (20)	K_2CO_3 (2.0)	89
16	CH_3CN	dppp (15)	K_2CO_3 (1.2)	88
17	CH_3CN	dppp (15)	K_2CO_3 (3.0)	91
18[f]	CH_3CN	dppp (15)	K_2CO_3 (1.2)	10

[a] Conditions: 2 mmol substrate, 1 MPa CO, 10 mol % $Pd(OAc)_2$, Ligand, Base, Solvent, 140 °C, 21 h.
[b] Isolated yield.
[c] 11 h.
[d] 27 h.
[e] 5 mol % $Pd(OAc)_2$.
[f] Reaction conducted at 120 °C.

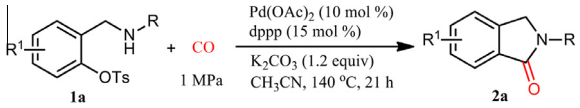
With the optimum reaction conditions in hand, we subsequently explored the scope of the reaction to various 2-(aminomethyl)aryl tosylates. As shown in Table 2, 2-(aminomethyl)aryl tosylates bearing various alkyl (entries 1–4), benzyl (entry 6, 7), and aryl (entries 8–13) substituents at the nitrogen atom were appropriate substrates for this methodology, and the corresponding isoindolinone derivatives were obtained in satisfactory to excellent yields. Aromatic amine bearing a strong electron-donating group afforded the corresponding isoindoline-1-one derivative in 94% yield (entry 12). Several functional groups are tolerated under these conditions (entries 7, 9, 10, 11, 12, 13). It is well-known that C–Cl bonds are generally more reactive than C–O bonds in metal-mediated transformations of carbon–heteroatom bonds via oxidative/reductive mechanism.[16] Significantly, products bearing chlorine were also obtained in 42% and 63% under the current conditions (Table 2, entries 7, 10). Substrates bearing electron-withdrawing groups such as F and CO_2CH_3 at the N-aromatic ring, could also give the desired products in moderate yields (Table 2, entries 11, 13). However, reaction with primary amine (2-(aminomethyl)phenyl tosylate) gave a complex mixture with a recovery of part starting material.

The effect of the substituent on the arene ring is examined. Regardless of whether a *m*-methyl or *p*-NEt_2 substituted aniline derivative was used, the reaction in the presence of $Pd(OAc)_2$ and dppp gave the corresponding isoindolinone products in satisfactory to excellent yields (entries 14–17). To our delight, 1-(aminomethyl)naphthalen-2-yl tosylates also proved to be suitable substrates for the cyclization, affording the desired 2-substituted-1*H*-benzo[*e*]isoindol-3(2*H*)-ones in good to excellent yields (entries 18–23). In addition, 2-(1-(ethylamino)ethyl)phenyl tosylate was also an appropriate substrate, and the corresponding 2-ethyl-3-methylisoindolin-1-one was obtained in satisfactory yield (entry 24). The structure of **2v** was further confirmed by the X-ray crystal diffraction analysis (Fig. 1).[17]

The presence of isoindoline-1,3-dione skeletons in naturally occurring compounds and synthetic materials,[18] coupled with the utility of isoindoline-1,3-dione-based reagents as intermediates[19] and ligands[20] in synthetic methodology, illustrates the need for efficient and versatile strategies for the construction of such types of heterocycles. However, cycloaminocarbonylation accessible to such N-heterocyclic skeletons from aryl tosylates have remained almost unexplored to date. Encouraged by the above results, the cycloaminocarbonylation of 2-(alkylcarbamoyl)phenyl 4-methylbenzenesulfonates with CO under the same conditions was investigated. As shown in Scheme 2, isoindoline-1,3-dione derivatives with various substitution patterns could also be synthesized in moderate to good yields.

In summary, we have developed an efficient and versatile method for the synthesis of isoindolinone derivatives by the Pd-catalyzed cycloaminocarbonylation of 2-(aminomethyl)aryl tosylates with carbon monoxide. Significantly, this methodology can also be applied in synthesis of isoindoline-1,3-diones from 2-(alkylcarbamoyl)aryl tosylates in good yields. The easy synthesis of 2-(aminomethyl)aryl and 2-(alkylcarbamoyl)aryl tosylates from cheap salicylaldehyde or salicylic acid as well as their low toxicity

Table 2
Cycloaminocarbonylation of 2-aminomethylaryl tosylates[a]



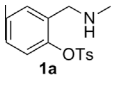
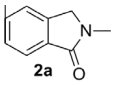
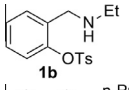
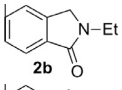
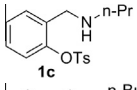
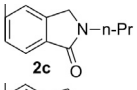
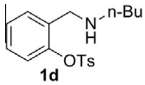
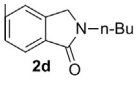
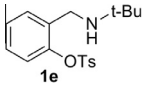
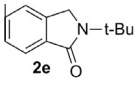
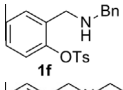
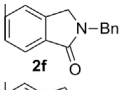
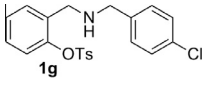
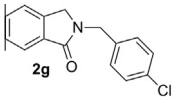
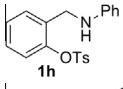
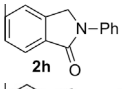
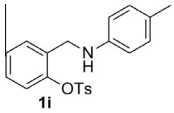
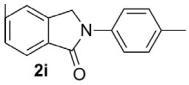
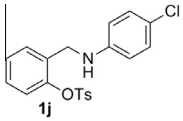
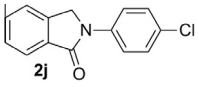
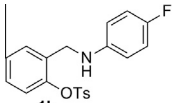
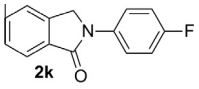
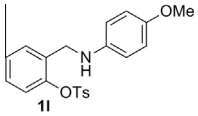
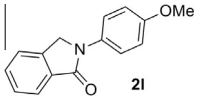
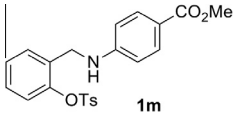
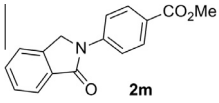
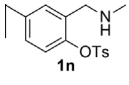
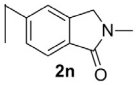
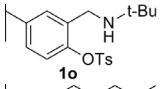
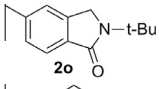
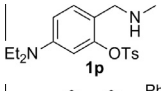
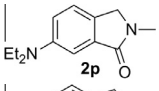
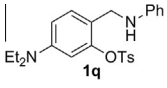
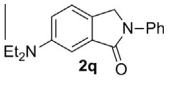
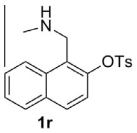
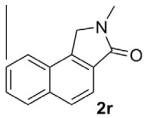
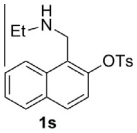
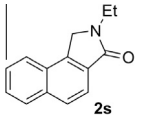
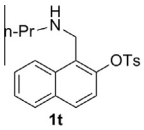
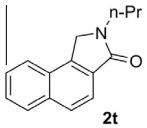
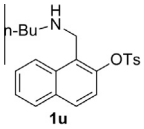
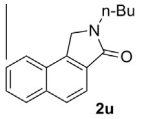
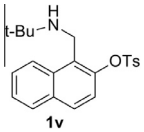
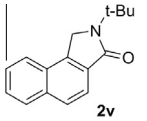
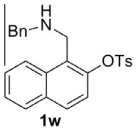
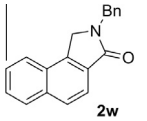
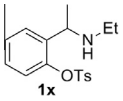
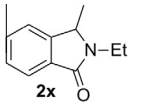
Entry	Substrate	Product	Yield[b] (%)
1	 1a	 2a	88
2	 1b	 2b	82
3	 1c	 2c	77
4	 1d	 2d	79
5	 1e	 2e	82
6	 1f	 2f	91
7	 1g	 2g	42
8	 1h	 2h	93
9	 1i	 2i	81
10	 1j	 2j	64
11	 1k	 2k	62
12	 1l	 2l	94
13	 1m	 2m	66
14	 1n	 2n	83
15	 1o	 2o	91
16	 1p	 2p	70
17	 1q	 2q	97

Table 2 (*continued*)

Entry	Substrate	Product	Yield[b] (%)
18	 **1r**	 **2r**	93
19	 **1s**	 **2s**	85
20	 **1t**	 **2t**	86
21	 **1u**	 **2u**	89
22	 **1v**	 **2v**	95
23	 **1w**	 **2w**	83
24	 **1x**	 **2x**	65

[a] Conditions: 2 mmol substrate, 10 mol % $Pd(OAc)_2$, 15 mol % dppp, 2.4 mmol K_2CO_3, 70 ml CH_3CN, 1 MPa CO, 140 °C, 21 h.
[b] Isolated yield.

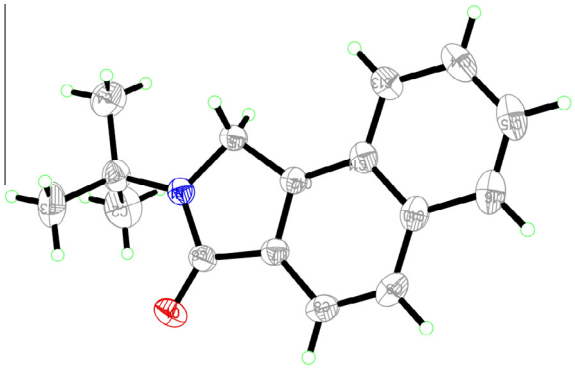
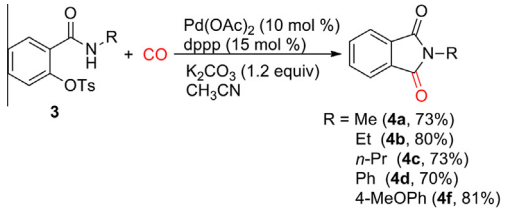


Figure 1. ORTEP diagram of the X-ray single-crystal structure of **2v**.



Scheme 2. Cycloaminocarbonylation of 2-(alkylcarbamoyl)phenyl toyslates.

makes them an attractive and practical alternative to commonly used organic halides as counterparts in aminocarbonylation protocols.

Experimental section

General procedure for the intramolecular cycloamino-carbonylation of 2-aminomethyl- and 2-alkylcarbamoylaryl tosylates.

2-(Aminomethyl)aryl tosylate (2 mmol), $Pd(OAc)_2$ (10 mol %), dppp (15 mol %), K_2CO_3 (2.4 mmol), and CH_3CN (70 ml) were charged in a 200 ml-autoclave. The autoclave was flushed and then pressurized with carbon monoxide to 1 MPa, the mixture was stirred at 140 °C for 21 h. The mixture was cooled to room temperature and vented to discharge the excess CO. After filtration, solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica gel with petroleum ether–ethyl acetate as the eluent to afford the desired product.

2-(*tert*-Butyl)-5-methylisoindolin-1-one (2o)

^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J = 7.7 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.19 (s, 1H), 4.40 (s, 2H), 2.43 (s, 3H), 1.55 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 141.4, 141.1, 131.9, 128.8, 122.9, 122.8, 54.1, 48.2, 27.9, 21.2. HRMS (ESI) Calcd for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388; Found: 204.1394.

6-(Diethylamino)-2-methylisoindolin-1-one (2p)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, J = 8.4 Hz, 1H), 7.09 (s, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.25 (s, 2H), 3.39 (q, J = 7.0 Hz, 4H), 3.17 (s, 3H), 1.16 (t, J = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 148.0, 134.0, 127.5, 123.0, 115.2, 105.6, 51.5, 44.6, 29.6, 12.4. HRMS (ESI) Calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1497; Found: 219.1497.

6-(Diethylamino)-2-phenylisoindolin-1-one (2q)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, J = 7.7 Hz, 2H), 7.40–7.44 (m, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.14–7.18 (m, 2H), 6.91 (dd, J = 8.4, 2.6 Hz, 1H), 4.76 (s, 2H), 3.42 (q, J = 7.0 Hz, 4H), 1.19 (t, J = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 148.2, 140.0, 134.3, 129.1, 126.7, 124.1, 123.2, 119.4, 116.3, 105.7, 50.2, 44.7, 12.4. HRMS (ESI) Calcd for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1654; Found: 281.1655.

2-Ethyl-1*H*-benzo[*e*]isoindol-3(2*H*)-one (2s)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85–7.97 (m, 4H), 7.59–7.62 (m, 2H), 4.72 (s, 2H), 3.77 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 140.1, 134.8, 130.6, 129.1, 128.9, 127.9, 127.5, 127.1, 123.0, 120.1, 48.5, 37.2, 13.9. HRMS (ESI) Calcd for $C_{14}H_{14}NO$ $[M+H]^+$: 212.1075; Found: 212.1079.

2-(*n*-Propyl)-1*H*-benzo[*e*]isoindol-3(2*H*)-one (2t)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84–7.97 (m, 4H), 7.58–7.60 (m, 2H), 4.70 (s, 2H), 3.67 (t, J = 7.3 Hz, 2H), 1.72–1.79 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 140.1, 134.8, 130.5, 129.1, 128.8, 127.9, 127.5, 127.1, 122.9, 120.1, 49.1, 44.1, 21.9, 11.3. HRMS (ESI) Calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1232; Found: 226.1228.

2-(*n*-Butyl)-1*H*-benzo[*e*]isoindol-3(2*H*)-one (2u)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92–7.96 (m, 1H), 7.82–7.89 (m, 3H), 7.56–7.59 (m, 2H), 4.67 (s, 2H), 3.69 (t, J = 7.3 Hz, 2H), 1.67–1.75 (m, 2H), 1.37–1.46 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 140.0, 134.7, 130.5, 129.1, 128.8, 127.9, 127.5, 127.0, 122.9, 120.0, 49.0, 42.1, 30.7, 20.0, 13.8. HRMS (ESI) Calcd for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1388; Found: 240.1383.

2-(*tert*-Butyl)-1*H*-benzo[*e*]isoindol-3(2*H*)-one (2v)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94–7.96 (m, 1H), 7.80–7.90 (m, 3H), 7.56–7.60 (m, 2H), 4.78 (s, 2H), 1.64 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 139.5, 134.8, 131.9, 129.2, 128.8, 127.8, 127.4, 127.0, 122.9, 119.9, 54.5, 47.6, 28.2. HRMS (ESI) Calcd for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1388; Found: 240.1394.

2-benzyl-1*H*-benzo[*e*]isoindol-3(2*H*)-one (2w)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92–7.96 (m, 3H), 7.76 (dd, J = 7.6, 2.0 Hz, 1H), 7.53–7.60 (m, 2H), 7.28–7.36 (m, 5H), 4.90 (s, 2H), 4.59 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 140.4, 137.2, 134.9, 130.0, 129.1, 128.9, 128.8, 128.2, 128.1, 127.9, 127.7, 127.1, 123.0, 120.2, 48.6, 46.5. HRMS (ESI) Calcd for $C_{19}H_{16}NO$ $[M+H]^+$: 274.1232; Found: 274.1236.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.088.

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