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Synthesis of Biaryls via Cross-Coupling Reaction of Arylboronic Acids with Aryl Chlorides Catalyzed by $NiCl_2$/Triphenylphosphine Complexes

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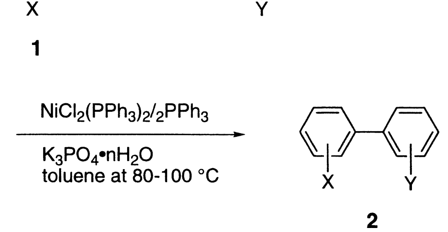
Abstract—The cross-coupling reaction of tolylboronic acids (1.3 equiv.) with chloroarenes in toluene was carried out at 80–100°C in the presence of a $NiCl_2/PPh_3$ catalyst (3 mol%) and $K_3PO_4{\cdot}nH_2O$ (2.6 equiv.). The reaction can be applied to various electron-deficient and -rich chloroarenes and is economical as the industrial process. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Various palladium complexes catalyze the cross-coupling reaction of arylboronic acids with aryl iodides, bromides or triflates for the synthesis of biaryls,[1] but economical and readily available chloroarenes are a desirable substrate for large-scale preparation in industry. Bulky and electron-donating phosphines such as tri(*t*-butyl)phosphine,[2] di(*t*-butyl)(2-phenylphenyl)phosphine,[3] and N-heterocyclic carbene[4] have recently been found to be highly effective as the ligand for the palladium-catalyzed coupling reactions of chloroarenes. However, the reduction of $NiCl_2$(dppf) with BuLi or DIBAL produces an active and economical catalyst for the cross-coupling reaction of arylboronic acids with aryl chlorides[5] and mesylates.[6] The nickel catalyst has an advantage over the palladium/phosphine complexes because of their high catalyst activity for various chloroarenes having an electron-withdrawing and -donating group, there is no appreciable side-reaction with the phosphine-bound aryls which is often unavoidable in the palladium-catalyzed coupling,[7] and the process is economical as recycling of the catalyst is not required. Here, we reinvestigated the nickel-catalyzed cross-coupling reaction of arylboronic acids with chloroarenes in the presence of $NiCl_2(PPh_3)_2/2PPh_3$, which had been carried out in dioxane in the presence of a $NiCl_2$(dppf) complex[5,6](Scheme 1). The economical $NiCl_2$–triphenylphosphine complexes were found to achieve higher catalyst efficiency than the $NiCl_2$/dppf complexes for various chloroarenes when the reaction was carried out in the presence of $K_3PO_4{\cdot}nH_2O$ suspended in toluene (Scheme 1).



Scheme 1. Biaryl coupling of chloroarenes with arylboronic acids.

Results and Discussion

Reaction conditions

The effects of the catalyst, reaction time, and temperature on the cross-coupling reaction of 3-chloroanisole with 4-tolylboronic acid in the presence of $K_3PO_4{\cdot}nH_2O$ (2.6 equiv.) are summarized in Table 1.

A 3 mol% of $NiCl_2(PPh_3)_2$ in toluene achieved 100% conversion within 2 h at 80°C which is apparently faster than the reaction catalyzed by $NiCl_2$(dppf) in dioxane (entry 1). The presence of 4 equiv. of PPh_3 to $NiCl_2$ can stabilize the labile nickel(0) species because the yield of the biaryl increased to 99% in the presence of additional two equivalents of PPh_3 (entry 2). The presence of further excess of ligand slowed down the reaction, but the addition of 4 and 10 equiv. of PPh_3 to $NiCl_2(PPh_3)_2$ also resulted in 98% and 94% yields after 6 h at 80°C. It was also interesting that the reduction of the nickel(II) complex to the nickel(0) prior to the coupling[5,6] was not necessary to generate an active catalyst, though it was critical in a similar reaction

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Keywords: coupling reactions; boron compounds; chloroarenes; biaryls.

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Table 1. Effect of catalysts (all reactions were carried out in toluene (3 ml) at 80°C by using 3-chloroanisole (1.0 mmol), 4-tolylB$(OH)_2$ (1.3 mmol), and a nickel catalyst)

Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield[a] (%)
1	$NiCl_2(PPh_3)_2$ (3)	80	2	90
2	$NiCl_2(PPh_3)_2/2PPh_3$ (3)	80	1.5	99
3	$NiCl_2(PPh_3)_2/2PPh_3$ (3)[b]	80	6	96
4	$NiCl_2(PPh_3)_2/2PPh_3$ (1)	80	2.5	99
5	$NiCl_2(PPh_3)_2/2PPh_3$ (0.5)	80	24	63
6	$NiCl_2(PPh_3)_2/2PPh_3$ (3)	60	6	8
7	$NiCl_2(PPh_3)_2/2PPh_3$ (3)	70	6	86
8	$NiCl_2(PPh_3)_2/2PPh_3$ (3)	90	2	99
9	$NiCl_2(PCy_3)_2$ (3)	80	2	94
10	$NiCl_2$(dppf) (3)	80	2	71

[a] GC yields.

[b] The catalyst was treated with DIBAL-H (2 equiv.) to reduce to the nickel(0) complex.

in dioxane (entry 3). A 1 mol% of catalyst gave a comparable yield to that obtained with 3 mol% catalyst (entry 4), whereas the 0.5 mol% loading resulted in 63% yield even after 24 h (entry 5). The reaction proceeded smoothly at over 80°C and was slow at lower than 70°C (entries 6–8). Although less effort was directed to optimization of phosphine ligands, an analogously high yield was achieved by the tri(cyclohexyl)phosphine complex (PCy_3) and the dppf complex was less effective than the PPh_3 complex (entries 9 and 10).

The effects of bases and solvents on the $NiCl_2/PPh_3$-catalyzed biaryl coupling are summarized in Table 2.

More than two equivalents of the finely powdered and hydrated potassium phosphate which contains 2–3 mol of water worked efficiently as the base, whereas the anhydrous phosphate and K_2CO_3 did not mediate the reaction (entries 1–5). On the other hand, no coupling reaction was observed in the presence of a strong base such as the finely powdered NaOH or KOH in toluene (entry 6), and the reaction resulted in significantly low yields when using $K_3PO_4{\cdot}nH_2O$ in polar solvents (entries 10 and 11). The reaction mixture turned to a milky emulsion suggesting the formation of nickel(II) hydroxide or nickel oxide. On the other hand, NaOH and KOH mediated the reaction when the nickel chloride complex was treated with DIBAL-H prior to the coupling reaction (entries 7 and 8). The nickel(II) chloride complex has an advantage over the nickel(0) complexes in its insensitivity to air, but care must be taken such that it is in situ reduced to the corresponding nickel(0) species when heating with $ArB(OH)_2$ and $K_3PO_4{\cdot}nH_2O$ in toluene.[8] $K_3PO_4{\cdot}nH_2O$ in polar solvent and KOH in toluene leads to the hydrolysis of the nickel chlorides (Scheme 2).

Table 2. Effect of bases and solvents (all reactions were carried out in toluene (3 ml) at 80°C in the presence of 3-chloroanisole (1.0 mmol), 4-tolylB$(OH)_2$ (1.3 mmol), and a nickel catalyst)

Entry	Base (equiv.)	Solvent	Time (h)	Yield[a] (%)
1	K_2CO_3 (2.6)	Toluene	6	38
2	$K_3PO_4{\cdot}nH_2O$ (2.6)	Toluene	6	99
3	$K_3PO_4{\cdot}nH_2O$ (2.6)	Toluene	2	99
4	$K_3PO_4{\cdot}nH_2O$ (2.0)	Toluene	6	96
5	$K_3PO_4{\cdot}nH_2O$ (1.0)	Toluene	6	74
6	KOH (2.6)	Toluene	6	0
7	KOH (2.6)[b]	Toluene	6	95
8	NaOH (2.6)[b]	Toluene	6	99
9	$K_3PO_4{\cdot}nH_2O$ (2.6)	Dioxane	2	77
10	$K_3PO_4{\cdot}nH_2O$ (2.6)	DME	2	7
11	$K_3PO_4{\cdot}nH_2O$ (2.6)	DMF	2	1

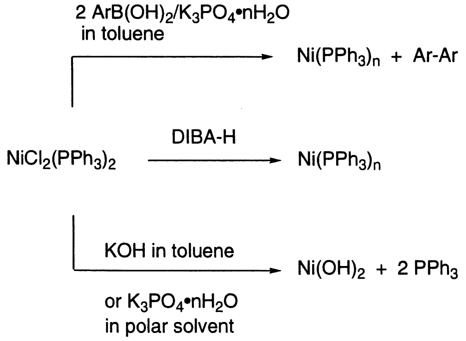
[a] GC yields.

[b] The catalyst was treated with DIBAL-H (2 equiv.) to reduce to the nickel(0) complex.

Scope and limitation

The synthesis of biaryls via the cross-coupling reaction of the representative chloroarenes is summarized in Table 3.

Chloroarenes having an electron-withdrawing group at the *para* or *meta* position gave excellent yields of biaryls exceeding 90% (entries 1–5). The electron-withdrawing group may accelerate the rates of oxidative addition and the transmetalation among the three steps involved in the catalytic cycle. The reaction was much slower in electron-rich chloroarenes, resulting in moderate yields at 80°C, but the reaction smoothly proceeded at 100°C (entries 6–8). The retarding effect of a neighboring hetero atom which chelates to the nickel(II) metal center was observed in some substrates including 2-(methoxycarbonyl)chlorobenzene, 2-chloropyridine, and 2-chloroquinoline (entries 4, 9, and 10). Such effect is not significant in the palladium-catalyzed cross-coupling reaction of arylboronic acids, but the



Scheme 2. Reduction of Ni(II) to Ni(0) complex.

Table 3. Synthesis of biaryls (all reactions were carried out in toluene (3 ml) at 80°C in the presence of chloroarene (1.0 mmol), 4-tolylB$(OH)_2$ (1.3 mmol), $K_3PO_4{\cdot}nH_2O$ (2.6 mmol), $NiCl_2(PPh_3)_2$ (0.03 mmol), and PPh_3 (0.06 mmol), unless otherwise noted)

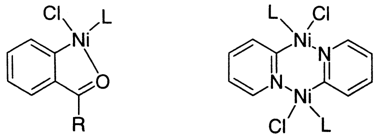
Entry	ArCl	Time (h)	Yield[a] (%)	
1	$4\text{-}NCC_6H_4Cl$	2	87	
2	$2\text{-}NCC_6H_4Cl$	2	97	
3	$4\text{-}OHCC_6H_4Cl$	2	(92)	
4	$2\text{-}MeO_2CC_6H_4Cl$	2	37	83[b]
5	$3\text{-}MeOC_6H_4Cl$	2	(99)	
6	$4\text{-}MeOCH_2OC_6H_4Cl$	2	64	74[b]
7	$4\text{-}H_2NC_6H_4Cl$	2	64	81[b]
8	$4\text{-}Me_2NC_6H_4Cl$	2	41	68[c]
9	2-chloropyridine	16	15[d]	
10	2-chloroquinoline	16	50	88[d]

[a] Isolated yields and GC yields are in parentheses.

[b] At 100°C for 2 h.

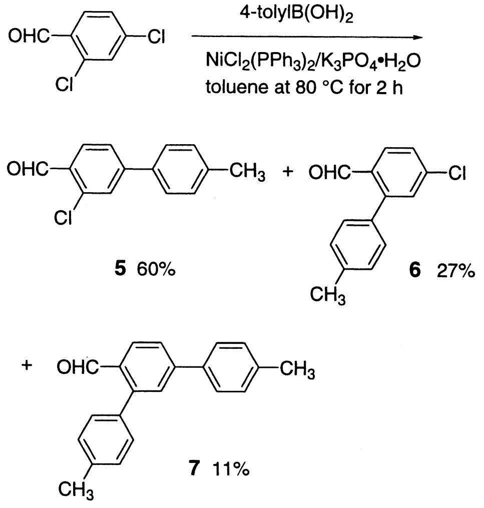
[c] At 100°C for 8 h.

[d] At 100°C for 16 h in the presence of 4-tolylB$(OH)_2$ (2 mmol).



3 R= H, OMe **4**

Scheme 3. Retarding effect of neighboring group.



Scheme 4. Regioselectivity in 2,4-dichlorobenzaldehyde.

nickel(II) intermediates generated by oxidative addition of chloroarene seems to be more Lewis acidic than those generated from the palladium catalysts (Scheme 3). The intra- or intermolecular coordination of the neighboring hetero atom[9] may retard either the transmetalation step or the reductive elimination step.

The regioselectivity in the coupling reaction of 2,4-dichlorobenzaldehyde is shown in Scheme 4.

The nickel-catalyzed reaction yielded *para*- and *ortho*-coupling products in a ratio of 69: 31 accompanied with a di-coupling product. The yield of the di-coupling product was dependent on the stoichiometry of tolylboronic acid, but all attempts at the selective coupling at the *para* position were unsuccessful. However, an analogous reaction catalyzed by a $Pd(dba)_2$/phosphine catalyst exhibited the opposite regioselectivity favoring the *ortho*-coupling: **5**/**6**=50/50 with PPh_3, 34/66 with PCy_3, 34/66 with dppb, and 36/64 with dppf ligand.

Experimental

Reagents

A green crystal of $NiCl_2(PPh_3)_2$ was synthesized from $NiCl_2{\cdot}6H_2O$ and PPh_3 in hot acetic acid.[10] The reaction of $NiCl_2{\cdot}6H_2O$ with a commercially available phosphine in benzene at 50°C gave the nickel chloride complexes with dppf (1,1′-bis(diphenylphosphino)ferrocene) and tricyclohexylphosphine (PCy_3).[11] 4-Tolylboronic acid[12] and chloroarenes were commercially available. $K_3PO_4{\cdot}nH_2O$ (n=2–3) from Nakalai Tesque Co. was used directly. Dioxane and toluene were distilled from benzophenone ketyl.

Effect of catalysts (Table 1)

The flask was charged with a $NiCl_2$ complex (0.005–0.03 mmol), a phosphine ligand (if used, 2 equiv. of PPh_3), 4-tolylboronic acid (1.3 mmol), and $K_3PO_4{\cdot}nH_2O$ (2.6 mmol), and then flushed with argon. Toluene (3 ml) and 3-chloroanisole (1.0 mmol) were successively added to the flask, and the mixture was then stirred at the temperature for the period shown in Table 1.

Effects of base and solvents (Table 2)

The flask was charged with $NiCl_2(PPh_3)_2$ (0.03 mmol), PPh_3 (0.06 mmol), 4-tolylboronic acid (1.3 mmol), and a base (1.0–2.6 mmol), and then flushed with argon. A solvent (3 ml) and 3-chloroanisole (1.0 mmol) were successively added to the flask, and the mixture was then stirred at 80°C for the period shown in Table 2. Potassium and sodium hydroxide were ground to a powder before use (entries 6–8). The reduction of the $NiCl_2$ complex was carried out as follows (entries 7 and 8). The flask charged with $NiCl_2(PPh_3)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and toluene (3 ml) under argon. The mixture was treated with *n*-BuLi in hexane (4 equiv.) at room temperature for 30 min to give a solution of the nickel(0) complex. *p*-Tolylboronic acid (1.3 mmol), 3-chloroanisole (1.0 mmol), and $K_3PO_4{\cdot}nH_2O$ (2.6 mmol) were added to the catalyst solution, and the resulting mixture was stirred for 6 h at 80°C.

Representative procedure (Table 3)

$NiCl_2(PPh_3)_2$ (0.03 mmol), PPh_3 (0.06 mmol), 4-tolylboronic acid (0.177 g, 1.3 mmol), and $K_3PO_4{\cdot}nH_2O$ (2.6 mmol) were added to a flask equipped with a magnetic stirring bar, a septum inlet, and reflux condenser. The flask was thoroughly flashed with argon and then charged with toluene (2 ml) and 3-chloroanisole (0.142 g, 1.0 mmol). The resulting mixture was stirred at 80°C for the period shown in Table 3. The product was extracted with toluene, washed with water and brine, and dried over $MgSO_4$. *The addition of alkaline hydrogen peroxide is a convenient way to oxidize the residual arylboronic acid to phenol and triphenylphosphine to the oxide. However, the oxidation should be absolutely avoided because the nickel forms an explosive peroxide.* Chromatography over silica gel with hexane/ethyl acetate gave 3-methoxy-4′-methylbiphenyl. IR (Nujol) 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.86 (s, 3H), 6.87 (dd, J=2.4, 8.0 Hz, 1H), 7.10 (dd, J=1.7, 2.4 Hz, 1H), 7.16 (d, J=7.8 Hz, 1H), 7.24 (d, J=7.9 Hz, 2H), 7.34 (dd, J=7.8, 8.0 Hz, 1H), 7.49 (d, J=7.9 Hz, 2H); MS *m/z* 155 (21), 167 (19), 187 (12), 198 (M^+, 100), 199 (18); exact mass calcd for $C_{14}H_{14}O$ 198.1045, found 198.1049.

The following biaryls were prepared by the above general procedure, unless otherwise noted.

4-Cyano-4′-methylbiphenyl. IR (Nujol) 2220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.28 (d, J=8.0 Hz, 2H), 7.49 (d, J=8.0 Hz, 2H), 7.66 (d, *J*=8.3 Hz, 2H) 7.70 (d, *J*=8.3 Hz, 2H); MS *m*/*z* 75 (3), 82 (6), 91 (8), 140 (4), 152 (4), 165 (16), 177 (7), 193 (M^+, 100); exact mass calcd for $C_{14}H_{11}N$ 193.0891, found 193.0888.

4-Formyl-4′-methylbiphenyl. IR (Nujol) 1710, 1200, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.29 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.0 Hz, 2H), 7.74 (d, *J*=8.3 Hz, 2H), 7.94 (d, *J*=8.3 Hz, 2H), 10.05 (s, 1H); MS *m*/*z*152 (29), 167 (22), 196 (M^+, 100), 197 (15); exact mass calcd for $C_{14}H_{12}O$ 196.0888, found 196.0878.

2-Cyano-4′-methylbiphenyl. IR (Nujol) 2300 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42, (s, 3H), 7.30 (d, *J*=8.0 Hz, 2H), 7.42 (dt, *J*=1.2, 7.7 Hz, 1H), 7.46 (d, *J*=8.0 Hz, 2H), 7.51 (d, *J*=7.7 Hz, 1H), 7.63 (dt, *J*=1.2, 7.7 Hz, 1H), 7.75 (d, *J*=7.7 Hz, 1H); MS *m*/*z* 63 (6), 82 (7), 91 (6), 96 (8), 165 (31), 193 (M^+, 100); exact mass calcd for $C_{14}H_{11}N$ 193.0891, found 193.0891.

2-Methoxycarbonyl-4′-methylbiphenyl. IR (Nujol) 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.66 (s, 3H), 7.18–7.24 (m, 4H), 7.36 (dd, *J*=1.4, 7.6 Hz, 1H), 7.38 (ddd, *J*=1.4, 7.6, 7.6 Hz, 1H), 7.51 (ddd, *J*=1.4, 7.6, 7.6 Hz, 1H), 7.80 (dd, *J*=1.4, 7.8 Hz, 1H); MS *m*/*z*76 (5), 98 (3), 115 (9), 128 (3), 139 (10), 152 (47), 167 (26), 195 (100), 226 (M^+, 73); exact mass calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.1003.

4-Methoxymethoxy-4′-methylbiphenyl. IR (Nujol) 1230, 1160, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.50 (s, 3H), 5.21 (s, 2H), 7.09 (d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.1 Hz, 2H), 7.44 (d, *J*=8.1 Hz, 2H), 7.50 (d, *J*=8.8 Hz, 2H); MS *m*/*z* 155 (9), 184 (100), 198 (65), 228 (M^+, 59); exact mass calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1159.

4-Amino-4′-methylbiphenyl. IR (Nujol) 1630, 1280 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.69 (s, 2H), 6.74 (d, *J*=8.5 Hz, 2H), 7.20 (d, *J*=7.9 Hz, 2H), 7.39 (d, *J*=8.5 Hz, 2H), 7.43 (d, *J*=7.9 Hz, 2H); MS *m*/*z* 155 (1), 167 (6), 182 (29), 183 (M^+, 100); exact mass calcd for $C_{13}H_{13}N$ 183.1048, found 183.1055.

4-(N, N-Dimethylamino)-4′-methylbiphenyl. IR (Nujol) 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.98 (s, 6H), 6.80 (d, *J*=8.8 Hz, 2H), 7.20 (d, *J*=8.1 Hz, 2H), 7.45 (d, *J*=8.1 Hz, 2H), 7.48 (d, *J*=8.8 Hz, 2H); MS *m*/*z* 91 (3), 105 (9), 167 (12), 195 (15), 211 (M^+, 100), 212 (16); exact mass calcd for $C_{15}H_{17}N$ 211.1361, found 211.1386.

2-(4-Methylphenyl)quinoline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.33 (d, *J*=8.1 Hz, 2H), 7.49–7.53 (m, 1H), 7.70–7.74 (m, 1H), 7.81 (d, *J*=8.1 Hz, 1H), 7.86 (d, *J*=8.5 Hz, 1H), 8.07 (d, *J*=8.1 Hz, 2H), 8.16 (d, *J*=8.5 Hz, 1H), 8.20 (d, *J*=8.5 Hz, 1H); MS *m*/*z* 95 (5), 109 (6), 204 (7), 219 (M^+, 100), 220 (18); exact mass calcd for $C_{16}H_{13}N$ 219.1048, found 219.1049.

2-(4-Methylphenyl)pyridine. IR (Nujol) 1590, 1560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ 2.40 (s, 3H), 7.20 (dd, *J*=4.8, 6.6 Hz, 1H), 7.27 (d, *J*=8.3 Hz, 2H), 7.67–7.72 (m, 2H), 7.88 (d, *J*=8.3 Hz, 2H), 8.67 (d, *J*=2.6 Hz, 1H); MS *m*/*z* 77 (5), 78 (6), 83 (14), 91 (11), 154 (10), 169 (M^+, 100); exact mass calcd for $C_{12}H_{11}N$ 169.0891, found 169.0891.

2-Chloro-4-(4-methylphenyl)benzaldehyde. IR (Nujol) 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.29 (d, *J*=8.2 Hz, 2H), 7.52 (d, *J*=8.2 Hz, 2H), 7.60 (dd, *J*=1.6, 8.1 Hz, 1H), 7.66 (d, *J*=1.6 Hz, 1H), 7.98 (d, *J*=8.1 Hz, 1H), 10.49 (s, 1H); MS *m*/*z* 139 (1), 166 (23), 201 (3), 229 (96), 230 (M^+, 100); exact mass calcd for $C_{14}H_{11}ClO$ 230.0498, found 230.0487.

2,4-Di(4-methylphenyl)benzaldehyde. IR (Nujol) 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.44 (s, 3H), 7.27–7.34 (m, 6H), 7.57 (d, *J*=8.3 Hz, 2H), 7.64 (d, *J*=1.7 Hz, 1H), 7.69 (dd, *J*=8.3, 1.7 Hz, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 10.01 (s, 1H); MS *m*/*z* 91 (1), 194 (2), 258 (2), 285 (61), 286 (M^+, 100); exact mass calcd for $C_{21}H_{18}O$ 286.1358, found 286.1355.

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