Preparation and Reactions of Functionalized Arylmagnesium Reagents

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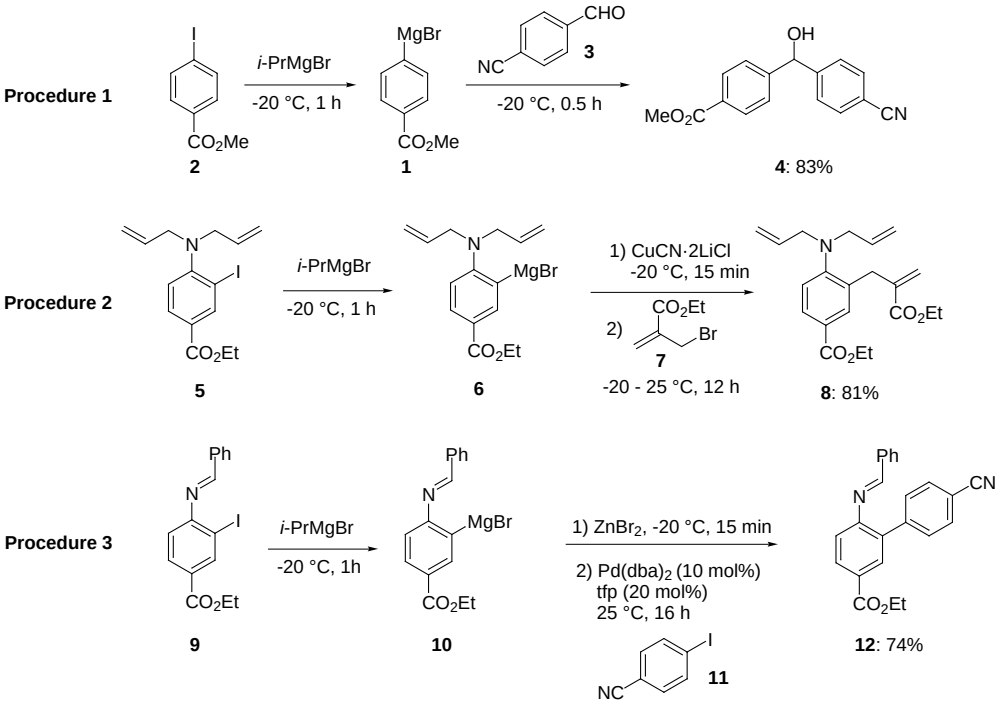
Abstract: Functionalized magnesium reagents have been prepared via an iodine-magnesium exchange. These reagents can be either trapped directly with aldehydes or transmetallated to copper or zinc to participate in cross-coupling reactions. The iodine-magnesium exchange, represent a unique method for the preparation of aryl and heteroaryl magnesium reagents.

Key words: functionalized magnesium reagents, iodine-magnesium exchange, cross-coupling, palladium



Scheme 1

Introduction

Polyfunctional organometallic reagents are important building blocks for the synthesis of complex target molecules.[1] In particular, organozinc reagents are known to tolerate a wide range of functional groups.[1,2] Recently, we have shown that a halogen-magnesium exchange[3] allows the preparation of arylmagnesium halides bearing sensitive functional groups such as an ester[4], nitrile, or imine[5] function. These unsaturated organometallic reagents combine a good functional group tolerance with an intrinsic high reactivity. By performing various stoichiometric or catalytic transmetallations, this reactivity can be fine-tuned, allowing optimum reaction conditions with numerous classes of electrophiles.

Scope and limitations

The mild conditions required for performing the iodine- or bromine-magnesium exchange[6,7] are compatible with several sensitive functionalities on the aryl halide. Thus, an ester or nitrile group is compatible with the generation of an arylmagnesium reagent via an iodine-magnesium ex-

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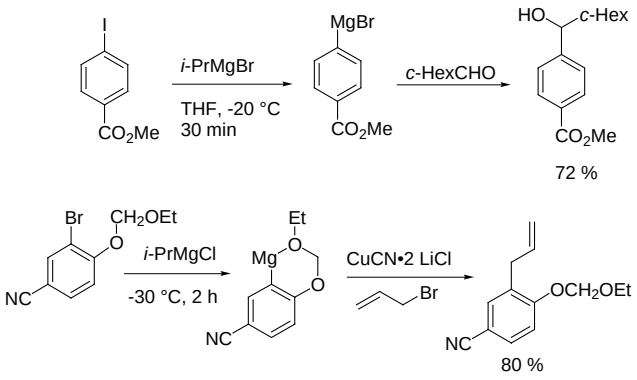
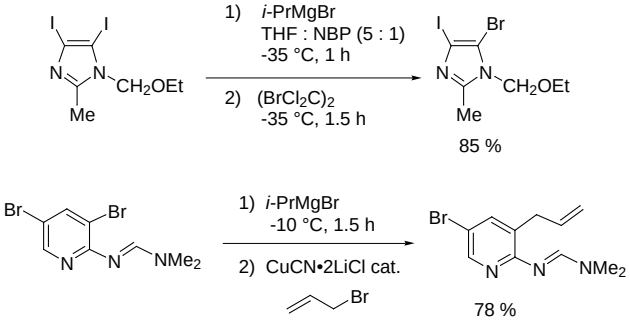
change, which is complete at –20 °C within a few hours. Under these mild conditions, no attack on the ester or nitrile group occurs (Scheme 1).



Scheme 2 Low temperature halogen-magnesium exchange.

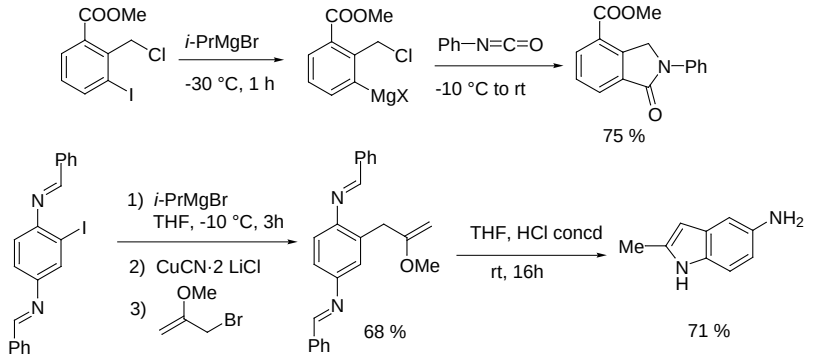
The rate of the iodine-magnesium exchange is significantly slower than the iodine-lithium exchange,[8] and it is observed that the nature of the aromatic or heteroaromatic ring strongly influences the rate of the exchange. The more electron-poor the aromatic ring, the faster is the exchange reaction. Also, the presence of chelating groups *ortho*- to the carbon-halogen bond strongly accelerates the exchange and allows the bromine-magnesium exchange to take place under milder conditions than usual. In general, iodine-magnesium exchange reactions are considerably faster than the corresponding bromine-magnesium exchange (Scheme 2). Selective mono-halogen-magnesium exchanges are observed with diiodo- or dibromo-aromatics. After the first exchange, the electron density of the ring increases to such an extent that no second exchange occurs (Scheme 2).



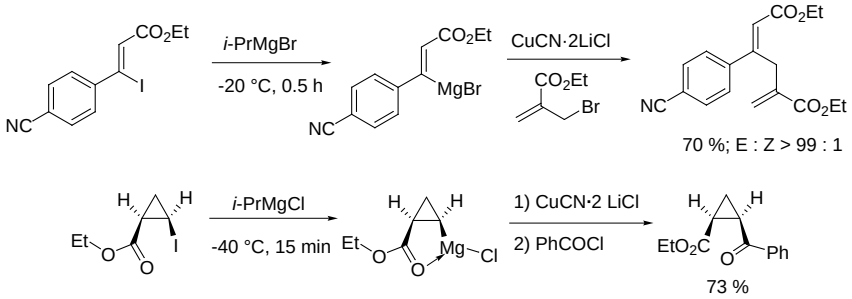
Scheme 3 Selective chelate directed halogen-magnesium exchange.

Polyfunctional aryl- and heteroaryl-magnesium reagents may readily undergo cyclization reactions[9] with suitable electrophiles, allowing the preparation of polyfunctional heterocycles (Scheme 4). Remarkably, the iodine-magnesium exchange can be extended to the preparation of functionalized alkenylmagnesium[10] or cyclopropylmagnesium[11] species (Scheme 5).

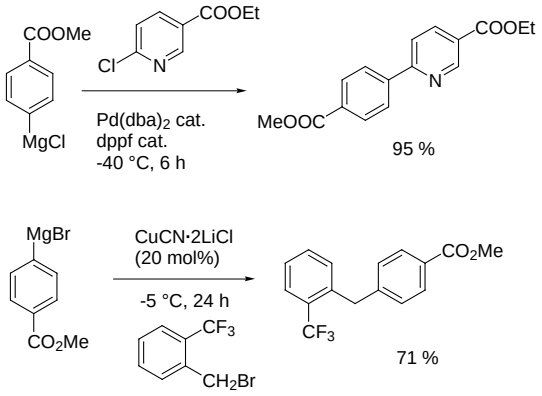
Functionalized arylmagnesium reagents readily participate in various transition metal catalyzed cross-coupling reactions.[12,13] Thus, 2-chloropyridines undergo exceptionally fast Pd(0)-catalyzed cross-couplings with functionalized arylmagnesium compounds. The high reaction rate may be explained by the formation of intermediate palladates.[13] Benzylic bromides and primary alkyl iodides undergo Cu(I)-mediated cross-couplings under mild conditions (Scheme 6).[12]



Scheme 4 Selective synthesis of functionalized heterocycles using functionalized Grignard-reagents.



Scheme 5 Preparation of functionalized alkenyl- and cyclopropyl-magnesium reagents.



Scheme 6 Pd(0) and Cu(I)-mediated cross-coupling of functionalized arylmagnesium reagent.

In summary, the iodine- or bromine-magnesium exchange considerably expands the scope of the preparation of functionalized organomagnesium compounds. A range of new Grignard reagents bearing various electron-withdrawing groups can be obtained by these methods. Many of these reagents are excellent precursors for performing ring closure reactions. Increasingly, applications in both complex natural product synthesis[14] and industrial processes are being reported in the literature.[15]

Procedures

Herein, we describe three typical synthetic procedures demonstrating the synthetic scope of functionalised organomagnesium compounds. In **Procedure 1**, we report the preparation of *p*-carbomethoxyphenylmagnesium bromide **1** starting from commercially available methyl 4-iodobenzoate (**2**) and its direct addition to a functionalized aromatic aldehyde, 4-cyanobenzaldehyde (**3**) leading to the polyfunctional benzhydryl alcohol **4** in 83% yield. In the second procedure (**Procedure 2**) the iodoaniline derivative[16] **5**, having the amino group protected as a diallyl derivative, is converted to the corresponding aminated Grignard reagent **6**. This magnesium reagent is then transmetallated to the corresponding copper derivative and allylated with ethyl (2-bromomethyl)acrylate[17] (**7**), leading to the polyfunctional aniline **8** in 81% yield. In the last procedure (**Procedure 3**), a different amino protecting group (imine) is used in the substrate and a subsequent palladium(0)-catalyzed cross-coupling is described. The iodoimine[18] **9** is readily converted to the magnesium derivative **10**, transmetallated to the corresponding zinc reagent and coupled in the presence of Pd(0) with 4-iodobenzonitrile **11**, leading to the functional biaryl **12** in 74% yield.

iso-Propylmagnesium Bromide

A dry, argon flushed, 500 mL round-bottom flask, equipped with a magnetic stirring bar and a 200 mL dropping funnel, was charged with magnesium turnings (10.8 g, 450 mmol), which were covered with anhyd THF (50 mL). Then 2-bromopropane (18.5 g, 150 mmol) was added dropwise at r.t. in THF (200 mL). After stirring overnight, the dropping funnel was replaced by a rubber septum. To separate the reagent from the remaining magnesium turnings, the Grignard solution was transferred via a transfer-needle into another dry, argon flushed, 500 mL Schlenk flask equipped with a rubber septum. For storage of the *iso*-propylmagnesium bromide solution, the rubber septum was replaced by a glass stopper. The concentration of *i*-PrMgBr was determined by the method of Paquette.[19]

Ethyl 4-(*N*,*N*-Diallylamino)-3-iodobenzoate (5)[16]

A 250 mL round-bottom flask, equipped with a magnetic stirring bar and a reflux condenser, was charged with ethyl 4-aminobenzoate (5.8 g, 20 mmol), allyl bromide (14.3 mL, 160 mmol) and Na_2CO_3 (8.5 g, 80 mmol). DMF (150 mL) was added and the reaction mixture was heated to 100 °C. After completion (6 h, monitored by TLC analysis) the reaction mixture was cooled to r.t. and poured into water (100 mL), extracted with Et_2O (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (pentane–Et_2O, 20:1, 200 g Merck Silica 60, 0.040–0.060 mm) to yield **7** as a pale yellow oil (5.6 g, 76%).

IR (KBr): 2980 (m), 1716 (s), 1590 (s), 1285 (s), 1252 (s), 1112 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 1.8 Hz, 1 H), 7.86 (dd, *J* = 1.8, 8.4 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 5.77–5.68 (m, 2 H), 5.13–5.04 (m, 4 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 3.64–3.61 (m, 4 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 141.0, 135.1, 130.2, 127.1, 123.2, 118.6, 97.7, 61.6, 55.8, 14.7.

MS (EI, 70 eV): *m/z* (%) = 371 (41), 326 (21), 244 (100), 130 (44).

Anal. Calcd for $C_{15}H_{18}O_2NI$: C, 48.53; H, 3.77; N, 4.89. Found: C, 48.15; H, 3.69; N, 4.80.

Ethyl 4-Amino-3-iodobenzoate[20]

To a 250 mL round-bottom flask, equipped with a magnetic stirring bar, charged with iodine (5.0 g, 20 mmol) and silver sulfate (6.22 g, 20 mmol) EtOH (100 mL) was added. Ethyl 4-aminobenzoate (3.30 g, 20 mmol) was then added and the reaction mixture was vigorously stirred until complete conversion (30 min, monitored by TLC analysis). The reaction mixture was filtered through a glass sinter and concentrated in vacuo. The residue was then taken up in CH_2Cl_2 (100 mL), washed twice with 5% NaOH solution (75 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (pentane–Et_2O, 9:1, 200 g Merck Silica 60, 0.040–0.060 mm) yielding ethyl 4-amino-3-iodobenzoate as an off-white powder (5.5 g, 94% yield); mp 83 °C.

IR (KBr): 3661 (m), 1687, (s), 1612 (s), 1590 (m), 1286 (s), 1248 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 1.8 Hz, 1 H), 7.73 (dd, *J* = 1.8, 8.4 Hz, 1 H), 6.62 (d, *J* = 8.4 Hz, 1 H), 4.43 (br s, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 151.0, 141.3, 131.3, 121.9, 113.5, 82.5, 61.1, 14.8.

MS (EI, 70 eV): *m/z* (%) = 291 (80), 263 (31), 246 (100), 218 (9), 91 (16).

Anal. Calcd for $C_9H_{10}O_2NI$: C, 37.14; H, 3.46; N, 4.81. Found: C, 37.11; H, 3.45; N, 4.81.

Ethyl 3-Iodo{[(*E*)-phenylmethylidene]amino}benzoate (9)[18]

Ethyl 4-amino-3-iodobenzoate (8.73 g, 30 mmol) was dissolved in anhyd toluene (60 mL), then benzaldehyde (3.82 g, 36 mmol) and

concd H_2SO_4 (a few drops) were added and the mixture heated to reflux with a Dean–Stark head and condenser until no more water was separated (approx. 2 h). The solution was filtered and concentrated in vacuo. Excess benzaldehyde was distilled off at 100 °C under vacuum using an oil pump, the resulting yellow oil crystallized upon standing. Recrystallization from Et_2O yielded the product as yellow needles. Yield (9.98 g, 87%); mp 73 °C.

IR (KBr): 3436 (m), 1702 (s), 1626 (s), 1578 (s), 1290 (s), 1252 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 8.46 (d, *J* = 1.8 Hz, 1 H), 8.19 (s, 1 H), 7.91 (dd, *J* = 1.8, 8.1 Hz, 1 H), 7.87 (m, 2 H), 7.44 (m, 3 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.3, 162.2, 157.4, 140.7, 135.8, 132.6, 131.3, 129.7, 129.2, 127.5, 118.5, 94.0, 61.6, 14.8.

MS (EI, 70 eV): *m/z* (%) = 379 (100), 350 (19), 334 (40), 178 (17).

Anal. Calcd for $C_{16}H_{14}O_2NI$: C, 50.68; H, 3.72; N, 3.69. Found: C, 50.60; H, 3.76; N, 3.65.

Methyl 4-[(4′-Cyanophenyl)(hydroxy)methyl]benzoate (4)

A dry and argon flushed 50 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with methyl 4-iodobenzoate (**2**: 788 mg, 3 mmol) in anhyd THF (6 mL) and cooled to –20 °C. *i*-PrMgBr (6.2 mL, 0.54 M in THF, 3.3 mmol) prepared as described above, was slowly added. After 1 h, the exchange was complete (as indicated by GC analysis of reaction aliquots) and 4-cyanobenzaldehyde (**3**: 584 mg, 4.5 mmol) was added as a solution in THF (4 mL). The reaction mixture was allowed to warm to room temperature over 30 min. The reaction mixture was quenched with MeOH (3 mL), poured into water (150 mL) and extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (pentane–EtOAc, 70:30, 50 g Merck Silica 60, 0.040–0.063 mm) yielding the alcohol **5** as a white solid. Yield (668 mg, 83%); mp: 153 °C.

IR (KBr): 3514 (s), 2955 (w), 2227 (s), 1712 (s), 1604 (m), 1434 (m), 1294 (s), 1190 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 5.63 (s, 1 H), 5.08 (bs, 1 H), 3.67 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 149.1, 148.4, 131.5, 129.1, 128.6, 126.7, 126.0, 118.2, 110.2, 73.8, 51.4.

MS (EI, 70 eV): *m/z* (%) = 267 (9), 252 (4), 236 (19), 208 (28), 190 (20), 163 (42), 137 (100), 130 (52), 104 (31), 77 (25).

Anal. Calcd for $C_{16}H_{13}O_3N$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.81; H, 4.74; N, 5.12.

Ethyl 4-(*N*,*N*-Diallylamino)-3-[2-(ethoxycarbonyl)-2-propenyl]-benzoate (8)

A dry, argon flushed 25 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with amine **5** (1.11 g, 3 mmol) in anhyd THF (3 mL) and cooled to –20 °C. *i*-PrMgBr (3 mL, 1.3 M in THF, 3.9 mmol) was slowly added. After 1 h, the exchange was complete (as indicated by TLC analysis). CuCN·2LiCl (3.0 mL, 1 M in THF, 3 mmol) was slowly added. After 30 min, ethyl 2-(bromomethyl)acrylate[17] (**7**; 1.15 g, 6 mmol) was added and the reaction mixture allowed to warm to r.t. overnight. The reaction mixture was quenched with NH_4Cl–NH_3, 9:1 (3 mL), poured into water (50 mL) and extracted with Et_2O (3 × 70 mL). The combined organic fractions were washed with brine (100 mL), then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (pentane–EtOAc, 95:5, 70 g Merck Silica 60, 0.040–0.060 mm) yielding the amine **8** as a pale yellow oil (868 mg, 81%).

IR (KBr): 2981 (w), 1715 (s), 1605 (m), 1250 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.72 (m, 2 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.18 (d, *J* = 1.5 Hz, 1 H), 5.71–5.62 (m, 2 H), 5.27 (d, *J* = 1.5 Hz, 1 H), 5.11–5.01 (m, 4 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.67 (s, 2 H), 3.54 (s, 2 H), 3.52 (s, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.19 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 166.5, 154.4, 139.9, 134.4, 133.7, 132.2, 128.2, 125.9, 124.9, 121.9, 177.4, 60.6, 60.5, 55.6, 33.1, 14.3, 14.1.

MS (EI, 70 eV): *m/z* (%) = 357 (4), 316 (100), 286 (79), 242 (44), 168 (25), 115 (18).

Anal. Calcd for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.42; H, 7.68; N, 3.86.

Ethyl 4′-Cyano-6-{[(*E*)-phenylmethylidene]amino}[1,1’-biphenyl]-3-carboxylate (12)

A dry, argon flushed 25 mL round-bottom flask, equipped with a magnetic stirring bar was charged with the imine **9** (1.11 g, 3 mmol) in anhyd THF (3 mL) and cooled to –20 °C. *i*-PrMgBr (3.0 mL, 1.3 M in THF, 3.9 mmol) was slowly added. After 1 h the exchange was complete (monitored by TLC analysis) and $ZnBr_2$ (2.0 mL, 1.5 M in THF (3 mmol)) was added. The reaction mixture was allowed to warm to r.t. Another dry, argon flushed 25 mL flask, equipped with a magnetic stirring bar, was charged with $Pd(dba)_2$[21] (87 mg, 0.15 mmol) and tfp[21] (69 mg, 0.30 mmol) in anhyd THF (3 mL). After formation of the active catalyst (indicated by a slight colour change of the solution from red to yellow) 4-iodobenzonitrile (**11**; 481 mg, 2.1 mmol) was added followed by the zinc reagent, via syringe. The reaction mixture was stirred at r.t. for 16 h, quenched with NH_4Cl (5 mL), poured into water (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic fractions were washed with brine (70 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (pentane–EtOAc–TEA, 20:1:1, 70 g Merck Silica 60, 0.040–0.060 mm) to yield the imine **12** as a pale yellow powder (581 mg, 74%); mp: 102 °C.

IR (KBr): 3433 (m), 2229 (w), 1710 (s), 1627 (m), 1595 (s), 1578 (m), 1242 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 8.35 (s, 1 H), 8.00 (m, 2 H), 7.67 (m, 2 H), 7.54 (m, 4 H), 7.38 (m, 3 H), 7.03 (d, *J* = 9.0 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 1.32 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.4, 162.2, 153.8, 143.9, 136.1, 133.8, 132.5, 132.0, 131.8, 131.4, 131.2, 129.5, 129.3, 128.6, 119.6, 119.4, 111.3, 61.6, 14.8.

MS (EI, 70 eV): *m/z* (%) = 354 (41), 277 (100), 249 (46), 177 (12).

HRMS calcd for $C_{23}H_{18}O_2N_2$: 354.1368. Found: 354.1357.

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