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# Palladium and copper catalyzed one-pot Sonogashira reaction of 2-nitroiodobenzenes with aryl acetylenes and subsequent regioselective hydration in water: synthesis of 2-(2-nitrophenyl)-1-aryl ethanones

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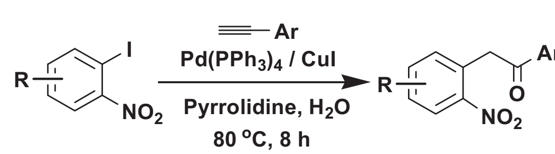
An attempted Sonogashira reaction of 2-nitroiodobenzene and phenyl acetylene catalyzed by $Pd(PPh_3)_4$/Cu in water in the presence of pyrrolidine proceeds with simultaneous regioselective hydration of the Sonogashira alkyne leading to the corresponding aryl ketone. A series of functionalized 2-(2-nitrophenyl)-1-aryl ethanones are obtained in high yields by this procedure.



During the course of our investigation we sought to have an access to selected Sonogashira products by the condensation of iodobenzenes and phenyl acetylenes. The reaction was performed using $Pd(PPh_3)_4$/CuI following a reported procedure.[1] Interestingly, we observed that when the reaction of 2-nitroiodobenzene and phenyl acetylene was continued for a longer period, the initially formed Sonogashira alkyne underwent regioselective hydration under the reaction conditions to produce the corresponding benzyl aryl ketone (Scheme 1) while other iodobenzenes furnished alkynes which remained inert towards hydration under identical reaction conditions. This prompted us to investigate this observation in more detail to find its general applicability and mechanism.

The hydration of alkynes to the corresponding carbonyl derivatives is a useful process.[2] Traditionally, this reaction was performed using mercury salts in strong acidic medium.[3] Later, several metal based catalysts containing Au,[4] Ru,[5] Rh,[6] Pt,[7], and Pd[8] have been employed. Significantly, hydration during Sonogashira reaction on the same pot was not observed in any of these reactions. We found only one report[9] where the alkynes formed by the reaction of aryl bromide and 3-butyn-1-ol using Pd-catalyst underwent partial hydration on treatment with 20% HCl. However, no reaction with aryl alkynes was addressed here.[9] Interestingly, in our procedure hydration occurs in basic medium under the standard Sonogashira conditions using Pd(0)/Cu(I) for the reaction of aryl iodides containing nitro functionality at the 2-position and aryl acetylenes. Toward better understanding of the reaction a series of experiments were carried out with a variation of substituents in the 2- and 4-position of aryl iodides and variation of solvent, time, and temperature for a typical Sonogashira reaction with phenyl acetylene. It was found that combined Sonogashira-hydration reaction was very much dependent on the substituent in the aryl iodides and reaction medium. The results are summarized in Table 1. The Sonogashira-hydration sequence leading to benzyl aryl ketone is successful for the reaction of 2-nitroiodobenzene and phenyl acetylene in water at 80 °C for 8 h (Table 1, entry 8, highlighted). Replacement of the nitro group by similar electron withdrawing functionalities such as –CN, –CHO, –COMe, –COOMe furnished the corresponding alkynes without further hydration. Interestingly, even 4-nitro iodobenzene provided the alkyne without any hydrated product under identical reaction conditions. The




**Scheme 1.** Hydration reaction followed by Sonogashira coupling.

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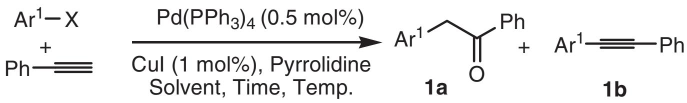
**Table 1**
Standardization of reaction conditions




| Entry | $Ar^1$ | Solvent | Time (h) | Temp (°C) | Yield[a] (%) | |
|---|---|---|---|---|---|---|
| | | | | | 1a | 1b |
| 1 | $o$-$NO_2C_6H_4$ | Toluene | 12 | 110 | – | 19 |
| 2 | $o$-$NO_2C_6H_4$ | DMF | 12 | 110 | – | 78 |
| 3 | $o$-$NO_2C_6H_4$ | DMSO | 12 | 100 | – | 72 |
| 4 | $o$-$NO_2C_6H_4$ | THF | 12 | 70 | – | 56 |
| 5 | $o$-$NO_2C_6H_4$ | Dioxane | 12 | 110 | – | 66 |
| 6 | $o$-$NO_2C_6H_4$ | NMP | 12 | 110 | – | 71 |
| 7 | $o$-$NO_2C_6H_4$ | $H_2O$ | 12 | 100 | 81 | 8 |
| **8** | **$o$-$NO_2C_6H_4$** | **$H_2O$** | **8** | **80** | **81** | **5** |
| 9 | $o$-$NO_2C_6H_4$ | $H_2O$ | 8 | rt | – | – |
| 10 | $o$-CN $C_6H_4$ | $H_2O$ | 8 | 80 | – | 73 |
| 11 | $o$-$CHOC_6H_4$ | $H_2O$ | 8 | 80 | – | 74 |
| 12 | $o$-$COMeC_6H_4$ | $H_2O$ | 8 | 80 | – | 78 |
| 13 | $o$-$COOMeC_6H_4$ | $H_2O$ | 8 | 80 | – | 69 |
| 14 | $p$-$NO_2C_6H_4$ | $H_2O$ | 8 | 80 | – | 82 |
| 15 | $p$-CN $C_6H_4$ | $H_2O$ | 8 | 80 | – | 78 |

[a] Yields refer to those of pure products characterized by IR, $^1H$ NMR, and $^{13}C$ NMR spectroscopic data.

use of aprotic solvents such as toluene, DMF, DMSO, THF, dioxane, and NMP did not initiate hydration at all. Among all solvents, $H_2O$ is most suitable for Sonogashira as well as hydration.

The substituted aryl benzyl ketones are of much importance in organic synthesis and have been employed as precursors to a variety of useful molecules.[10] Specifically, 2-(2-nitrophenyl)-1-arylethanones are valuable intermediates in the synthesis of 2,3-*N*-substituted indoles.[11] Considering the importance of these compounds we focused our attention to develop a general method for their synthesis based on our observation of the Sonogashira reaction with 2-nitroiodobenzene.

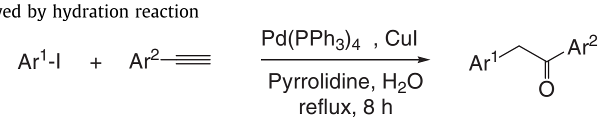
Thus, 2-nitroiodobenzene and substituted 2-nitroiodobenzenes were reacted with diversely substituted phenyl acetylenes catalyzed by $Pd(PPh_3)_4$/CuI in water under open atmosphere at 80 °C in the presence of pyrrolidine by a simple procedure[12] to provide the corresponding nitro-substituted benzyl aryl ketones in high yields. The results were reported in Table 2. The hydration is always highly regioselective giving only one product. The heteroaryl acetylenes (Table 2, entries 8 and 12) also underwent clean reactions. The products are obtained pure after simple work-up and several of these compounds are new being reported for the first time. However, a strong electron withdrawing group like nitro-substituted phenyl acetylenes did not undergo any hydration and the reaction stopped at the Sonogashira stage (Table 2, entry 14).

In general, the reactions are clean and high yielding although a small amount of (2–5%) dimers of the corresponding acetylenes and usual Sonogashira alkynes were also associated. These side-products were separated easily during purification and all the products are obtained in high purity and were characterized by spectroscopic data. Significantly, when an aliphatic acetylene (Table 2, entry 13) was employed in this reaction only the Sonogashira product was obtained and no hydrated ketone was formed even after prolonged reaction. This is possibly due to the absence of conjugation of the aliphatic moiety with the acetylenic triple bond favoring the hydration process. The hydration of alkynes in basic reaction medium by this procedure, which usually requires acidic conditions, is also of much interest.

It is believed that the reaction proceeds through a usual Pd(0)-catalyzed Sonogashira pathway[9] to provide the alkyne **I** which then undergoes hydration catalyzed by Pd(II), generated in situ from Pd(0) by molecular oxygen.[13] To check this hypothesis when the reaction is performed under argon atmosphere the hydration step is greatly arrested reducing the hydrated product to the range of 30%. (It is likely that hydration proceeds to some extent because of the presence of traces of air in the reaction medium.) As $-NO_2$ group is vital for this reaction, its participation in controlling the hydration step is most likely. Thus it is proposed that the oxygen of $-NO_2$ functionality interacts with the Pd(II) complex of the alkyne to form an intermediate **II** which undergoes hydration via **III** to provide the aryl ketone in a regioselective manner (Scheme 2). The involvement of Pd(II) in the hydration process is established by an experiment where the alkyne **I** was subjected to hydration under identical reaction conditions using $Pd(PPh_3)_2Cl_2$ to give the same aryl ketone in comparative yield.

In conclusion, we have developed a general procedure for the synthesis of 2-(2-nitrophenyl)-1-aryl ethanones, useful precursors to indoles,[11] by a simple one-pot reaction of 2-nitroiodobenzene

**Table 2**
Palladium catalyzed Sonogashira coupling followed by hydration reaction



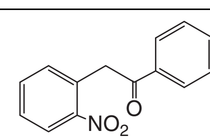
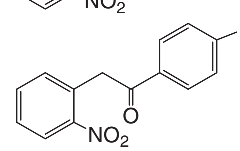
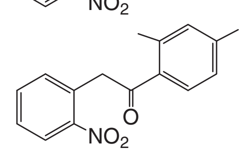
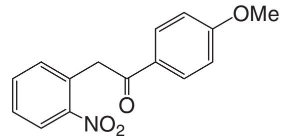
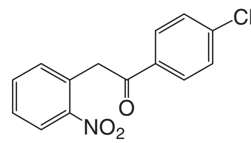
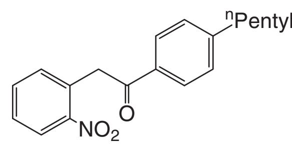
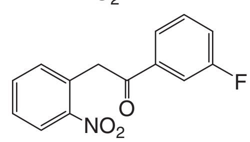
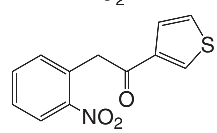
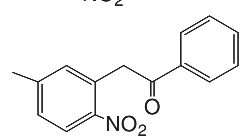
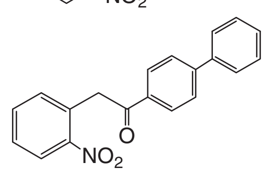
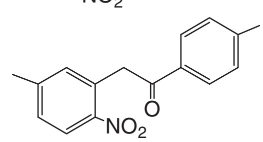
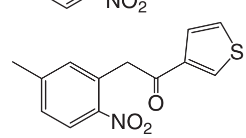
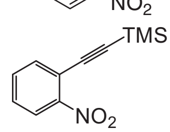
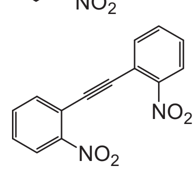
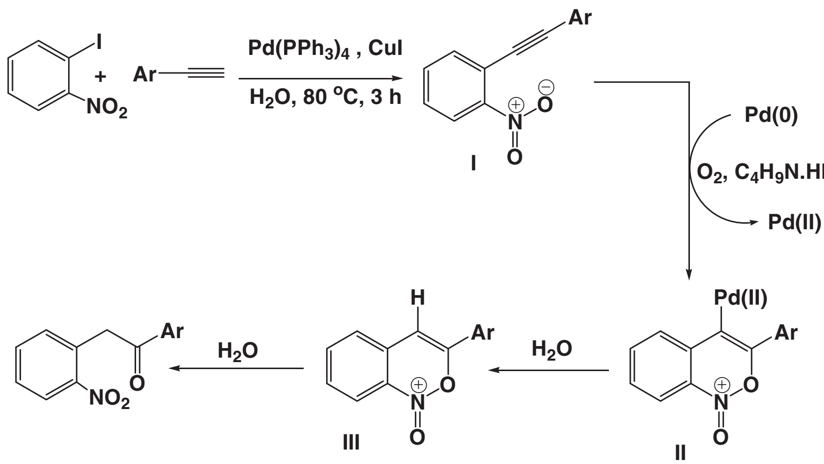

| Entry | $Ar^1$ | $Ar^2$ | Time (h) | Product | Yield (%)[a] | Refs. |
|---|---|---|---|---|---|---|
| 1 | $o$-$NO_2C_6H_4$ | Ph | 8 |   | 81 | 14 |
| 2 | $o$-$NO_2C_6H_4$ | 4Me-$C_6H_4$ | 8 |   | 84 | 15 |
| 3 | $o$-$NO_2C_6H_4$ | 2,4-Di$MeC_6H_4$ | 8 |   | 83 | |

**Table 2** (*continued*)

| Entry | Ar[1] | Ar[2] | Time (h) | Product | Yield (%)[a] | Refs. |
|---|---|---|---|---|---|---|
| 4 | *o*-$NO_2C_6H_4$ | 4-OMe-$C_6H_4$ | 8 |  | 86 | 15 |
| 5 | *o*-$NO_2C_6H_4$ | 4-$ClC_6H_4$ | 8 |  | 81 | 15 |
| 6 | *o*-$NO_2C_6H_4$ | 4-$^n$Pentyl$C_6H_4$ | 8 |  | 82 | |
| 7 | *o*-$NO_2C_6H_4$ | 3-$FC_6H_4$ | 10 |  | 78 | |
| 8 | *o*-$NO_2C_6H_4$ | 3-Thiophenyl | 8 |  | 85 | |
| 9 | 2-$NO_2$,5-$MeC_6H_3$ | Ph | 8 |  | 82 | |
| 10 | *o*-$NO_2C_6H_4$ | 4-$PhC_6H_4$ | 10 |  | 76 | |
| 11 | 2-$NO_2$,5-$MeC_6H_3$ | 4Me-$C_6H_4$ | 8 |  | 86 | |
| 12 | 2-$NO_2$,5-$MeC_6H_3$ | 3-Thiophenyl | 8 |  | 85 | |
| 13 | *o*-$COOMeC_6H_4$ | TMS | 8 |  | 56 | 16[b] |
| 14 | *o*-$NO_2C_6H_4$ | *o*-$NO_2C_6H_4$ | 8 |  | 38 | 17[c] |

[a] Yields refer to those of purified products characterized by IR, $^1$H, and $^{13}$C NMR spectroscopic data.
[b] Sonogashira product was formed together with acetylene dimer (23%).
[c] Only Sonogashira product was formed.

and aryl acetylenes in water catalyzed by $Pd(PPh_3)_4$/CuI involving Sonogashira coupling followed by hydration in the same pot. The significant features of this procedure are simplicity in operation, excellent regioselectivity, reaction in water, and high yields. To the best of our knowledge, this is the first report of Sonogashira coupling of 2-nitroiodobenzene and aryl alkynes in water involving hydration of the triple bond in the basic reaction media which leads to the formation of 2-(2-nitrophenyl)-1-aryl ethanones and




**Scheme 2.** Plausible mechanism.

we believe, this will make an important addition to organic synthesis.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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.2013.05.021.

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12. Representative experimental procedure for Sonogashira coupling and hydration of 2-iodonitrobenzene with phenyl acetylene (Table 1, entry 1). To a stirred mixture of 2-iodonitrobenzene (249 mg, 1.0 mmol), phenyl acetylene (153 mg, 1.5 mmol), pyrrolidine (142 mg, 2 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 equiv) and CuI (2 mg, 1 mol %) were added followed by water (5 mL). The reaction mixture was then stirred at 80 °C (oil bath temperature) for 8 h (TLC) and extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated to leave the crude product which was purified by column chromatography over silica gel with hexane–ethyl acetate (90:10) as eluent to furnish pure 2-(2-nitrophenyl)-1-phenylethanone as a yellowish viscous liquid (195 mg, 81%); IR (neat) 3055, 2891, 2837, 1688, 1590, 1503, 1341, 1212, 834 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 4.70 (s, 3H), 7.30 (d, $J$ = 7.5 Hz, 1H), 7.43–7.48 (m, 3H), 7.53–7.59 (m, 2H), 8.01 (d, $J$ = 12.5 Hz, 2H), 8.10 (d, $J$ = 14.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 44.2, 125.3 (2C), 128.3, 128.5, 128.8 (2C), 130.7, 133.6, 133.7, 133.8, 136.5, 149.1, 195.5. These data are in good agreement with those of an authentic sample.[14]
This procedure was followed for the synthesis of all the products listed in Table 2. The known compounds were identified by comparison of their IR, $^1H$ NMR, $^{13}C$ NMR, and HRMS spectral data with those reported (see references in Table 2). The unknown products (Table 2, entries 3, 6–13) were properly characterized by their spectroscopic (IR, $^1H$ NMR, $^{13}C$ NMR, and HRMS) data which are provided below.
1-(2,4-dimethylphenyl)-2-(2-nitrophenyl)ethanone (Table 2, entry 3): yellow solid; mp 81 °C; IR (KBr): 2924, 2852, 1684, 1521, 1517, 1350, 1311, 1173, 977 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 2.30 (s, 3H), 2.33 (s, 3H), 4.53 (s, 3H), 7.05 (d, $J$ = 8.0 Hz, 1H), 7.12 (d, $J$ = 7.5 Hz, 1H), 7.23 (d, $J$ = 8.0 Hz, 1H), 7.50 (t, $J$ = 7.5 Hz, 1H), 7.53 (s, 1H), 8.04 (d, $J$ = 8.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 20.8, 21.1, 46.9, 125.3, 128.4, 129.2, 131.0, 132.1, 132.5, 133.5, 133.8, 135.4, 135.7, 137.1, 149.1, 199.0; HRMS calcd for $C_{16}H_{15}NO_3$ ($M+Na^+$): 292.0950; found: 292.0951.
2-(2-nitrophenyl)-1-(4-pentylphenyl)ethanone (Table 2, entry 6): yellow solid; mp 85–87 °C; IR (KBr): 3343, 3119, 2953, 2852, 1678, 1604, 1524, 1338, 1221, 1180 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.91 (t, $J$ = 6.5 Hz, 3H), 1.31–1.39 (m, 4H), 1.62–1.68 (m, 2H), 2.68 (t, $J$ = 7.5 Hz, 2H), 4.71 (s, 2H), 7.28–7.35 (m, 3H), 7.47 (t, $J$ = 8.0 Hz, 1H), 7.60 (t, $J$ = 7.5 Hz, 1H), 7.95 (d, $J$ = 8.0 Hz, 2H), 8.14 (d, $J$ = 8.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 22.6, 30.9, 31.5, 36.1, 44.1, 125.3, 128.4, 128.5, 128.9, 130.9, 133.5, 133.7, 134.3, 149.3, 149.4, 195.1; HRMS calcd for $C_{19}H_{21}NO_3$ ($M+Na^+$): 312.1600; found: 312.1593.
1-(3-fluorophenyl)-2-(2-nitrophenyl)ethanone (Table 2, entry 7): yellow solid; mp 83 °C; IR (KBr): 3358, 3085, 1687, 1588, 1524, 1445, 1336, 1249, 1150 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 4.70 (s, 2H), 7.30–7.34 (m, 2H), 7.45–7.52 (m, 2H), 7.59–7.65 (m, 1H), 7.68–7.72 (m, 1H), 7.81–7.84 (m, 1H), 8.14–8.17 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 44.6, 115.3 (d, $J$ = 21.7 Hz, 1C), 120.8 (d, $J$ = 21 Hz, 1C), 124.3 (d, $J$ = 3.0 Hz, 1C), 125.6, 128.9 (2C), 130.7 (t, $J$ = 7.5 Hz, 1C), 133.9 (d, $J$ = 2.3 Hz, 1C), 138.8 (d, $J$ = 6.0 Hz, 1C), 149.2, 163.2 (d, $J$ = 246.8 Hz, 1C), 194.5; HRMS calcd for $C_{14}H_{10}FNO_3$ ($M+H^+$): 260.0723; found: 260.0718.
2-(2-nitrophenyl)-1-(thiophen-3-yl)ethanone (Table 2, entry 8): dark grey solid; mp 91–93 °C; IR (KBr): 3107, 2920, 2852, 1678, 1612, 1521, 1414, 1334, 1232, 1175 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 4.63 (s, 2H), 7.34–7.36 (m, 2H), 7.46–7.49 (m, 1H), 7.58–7.61 (m, 2H), 8.13 (d, $J$ = 4.5 Hz, 1H), 8.17–8.18 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) 45.1, 125.3, 126.7, 127.1, 128.5, 130.3, 132.5, 133.6, 133.7, 141.6, 149.2, 189.6; HRMS calcd for $C_{12}H_9NO_3S$ ($M+H^+$): 248.0381; found: 248.0376.
2-(5-methyl-2-nitrophenyl)-1-phenylethanone (Table 2, entry 9): yellow solid; mp 105–106 °C; IR (KBr): 3059, 2897, 1686, 1591, 1508, 1445, 1339, 1217, 1076 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 2.55 (s, 3H), 4.82 (s, 2H), 7.26 (s, 1H), 7.38 (d, $J$ = 8.5 Hz, 1H), 7.62 (t, $J$ = 8.0 Hz, 2H), 7.73 (t, $J$ = 7.5 Hz, 1H), 8.16 (d, $J$ = 7.5 Hz, 2H), 8.20 (d, $J$ = 8.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 21.4, 44.3, 125.4, 128.2 (2C), 128.7 (2C), 129.0, 130.8, 133.4, 134.4, 136.6, 144.9, 146.7, 195.7; HRMS calcd for $C_{15}H_{13}NO_3$ ($M+Na^+$): 278.0793; found: 278.0792.
2-(2-nitrophenyl)-1-(1,1′ biphenyl)phenylethanone (Table 2, entry 10): yellow solid; mp 113–115 °C; IR (KBr): 3059, 1680, 1602, 1521, 1402, 1342, 1197, 997 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 4.70 (s, 2H), 7.30–7.36 (m, 2H), 7.40–7.45 (m, 3H), 7.52–7.59 (m, 3H), 7.66 (t, $J$ = 8.5 Hz, 1H), 8.04 (t, $J$ = 8 Hz, 2H), 8.10 (t, $J$ = 8.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 44.2, 125.5, 127.5 (2C), 127.6 (2C), 128.4, 128.5, 129.0 (2C), 129.1 (2C), 130.8, 133.6, 133.8, 135.4, 140.0, 146.4, 149.2, 195.1; HRMS calcd for $C_{20}H_{15}NO_3$ ($M+Na^+$): 340.0950; found: 340.0950.
2-(5-methyl-2-nitrophenyl)-1-*p*-tolylethanone (Table 2, entry 11): light yellow solid; mp 110–111 °C; IR (KBr): 3051, 2913, 1681, 1606, 1588, 1514,

1336, 1206, 1001 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 2.56 (s, 3H), 4.80 (s, 2H), 7.26 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 2H), 8.20 (d, *J* = 8.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 21.4, 21.7, 44.2, 125.5, 128.4 (2C), 128.9, 129.4 (2C), 131.0, 134.4, 144.3, 144.8, 146.8, 195.3; HRMS calcd for $C_{16}H_{15}NO_3$ (M+$H^+$): 270.1130; found: 270.1124.

2-(5-methyl-2-nitrophenyl)-1-(thiophen-3-yl)ethanone (Table 2, entry 12): dark grey solid; mp 91–92 °C; IR (KBr): 3133, 3081, 1673, 1558, 1510, 1403, 1336, 1244, 1178 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 2.44 (s, 3H), 4.61 (s, 2H), 7.15 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.35–7.37 (m, 1H), 7.60 (d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 8.19 (t, *J* = 3.5 Hz, 1H), 8.19 (t, *J* = 3.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$,125 MHz) $\delta$ 21.5, 45.3, 125.5, 126.6, 127.1, 129.1, 130.4, 132.5, 134.4, 141.7, 144.9, 146.7, 189.9; HRMS calcd for $C_{13}H_{11}NO_3S$ (M+$H^+$): 262.0538; found: 262.0534.

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