Nickel Catalyzed Electrochemical Heteroarylation of Activated Olefins

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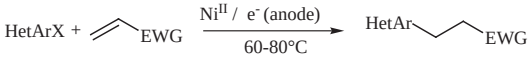
Abstract: Conjugate addition reaction of heteroaryl halides to activated olefins has been successfully achieved by nickel catalysis combined with the consumable anode procedure and provides access to various functionalized heteroaryl compounds with potential biological activity.

Key words: catalysis, nickel, heteroaryl halide, electrochemistry, alkenes

Functionalized heteroaromatic structures are important building blocks for the synthesis of biologically active molecules as pharmaceuticals or agrochemicals. Heteroaromatic compounds have also found applications in material science and supramolecular chemistry. One general access to functionalized heteroaryl compounds uses heteroaryl metal intermediates. These can be obtained either by directed hydrogen-metal exchange[1a–b] (lithium or magnesium) or by halogen-metal exchange[2a–d] (e.g. with *i*PrMgX or BuLi) eventually followed by transmetallation with CuCN,[2d] $ZnCl_2$[3a] or nBu_3SnCl.[3a] These intermediates are further reacted with electrophiles in coupling or addition reactions eventually in the presence of transition metal catalyst. Pyridyl, [2a–b] imidazoyl, [3a–b] or pyrazoyl[4] halides were functionalized according to these two-step procedures. Though efficient, these procedures usually require very restrictive reaction conditions, notably low or even quite low temperature.[1,2c,d] Alternatively, cross-coupling reactions[5a–5b] mediated by transition metal catalysts involving organometallics and heteroaryl halides have been described in the literature for alkylation and arylation of heterocyclic compounds.

More importantly, however, transition metal catalysis offers very interesting prospects in that one-pot procedures can be carried out directly from readily available heteroaryl halides when the catalytic process can be combined with a reducing agent operating in situ.[6] We have already developed this approach by combining the transition metal catalyzed electroreductive activation of organic halides and the use of a sacrificial anode. We have applied this methodology to aryl or alkenyl halides in cross-coupling with organic halides[7] in addition reaction to aldehydes[8] or to activated olefins[9a–9c] and more recently to heteroaryl halides in homo- and cross-coupling reactions.[10]

As part of our investigations devoted to the heteroaryl halide chemistry, we report in this paper the heteroarylation of activated olefins mediated by nickel catalysis (Scheme 1). This straightforward, mild, and efficient reaction is compatible with a large number of functional groups[9] and easily implemented.[11]

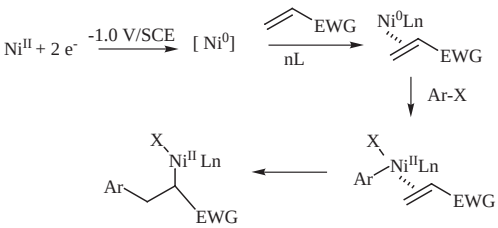


EWG: electrowithdrawing group

Scheme 1

This reaction is a very convenient method to tether a functional group separated by two methylene groups to an aryl moiety with the aim of either modifying the physical properties of the substrate (polar group) or enabling further grafting to another moiety.

The reaction mechanism (Scheme 2) includes *i*. the electrochemical reduction of $NiBr_2$ into Ni(0) which is stabilized in the solution by complexation to weak ligands (pyridine, acetonitrile, the activated olefin) along with the release of iron ions from anode oxidation, *ii*. the oxidative addition of ArX to Ni(0), *iii*. the insertion of activated olefin into the Ar–Ni bond.



Scheme 2

The final organonickel intermediate can be either protonated in situ to give the product and Ni(II) or converted into an alkyl iron intermediate by transmetallation with iron ions (Scheme 3).

The interest of heterocyclic structures in bioactive compounds prompted us to examine if this approach (Scheme 1) is compatible with the presence of heteroatoms (N, S, O) in the aromatic ring. The key points in this investigation are the nature and the number of heteroatoms in the aromatic ring, the nature of the halogen, as well as its position relative to the heteroatom.

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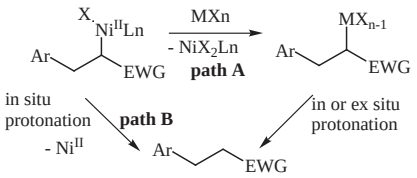


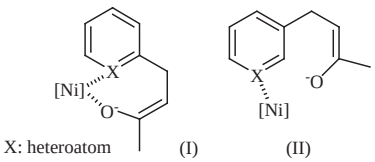
Scheme 3

We first investigated the reactivity of heteroaryl halides bearing a single heteroatom i.e. the 2- and 3-halo-derivatives of pyridine, quinoline, and thiophene. Methyl vinyl ketone (MVK) which is a good Michael acceptor in the arylation process[9b] was selected as the activated olefin and the conjugate addition reactions were first performed according to either of the two protocols previously reported, that is, in DMF–pyridine, 9:1[9a–b] (method A) or in DMF–acetonitrile, 1:1[9c] (method B).

The reactions are typically carried out in an undivided electrolysis cell flushed with argon and fitted with an iron or stainless steel rod as the anode and a concentric nickel foam as the cathode. A short preelectrolysis, conducted at constant current density (0.5 A/dm^2) involving the oxidation of the anode, along with the reduction of 1, 2-dibromoethane (0.7 mmol) added in the solvent mixture containing NBu_4Br–NBu_4I, is run at room temperature prior to the successive addition of the heteroaryl halide (1 equiv), MVK (2.5 equiv) and the catalyst precursor $NiBr_2 \cdot 3H_2O$ (0.1 equiv). We previously found that this short preelectrolysis[9c] enhances the yields thanks to the presence of iron salts at the beginning of the reaction. The electrolysis is conducted at constant current intensity (0.15 A) and at 60 °C until full consumption of the heteroaryl halide. The cathode potential throughout the electrolysis is at ca –1.0 V versus SCE.

In Table 1 are reported the results of the nickel-catalyzed electrochemical heteroarylation of MVK. In most cases the electrochemical conjugate addition reaction occurs affording the desired adduct with moderate to high yields. The main by-product is the reduction product of the heteroaryl halide. Table 1 allows us to make three preliminary remarks: *i*. when the halogen is α to the heteroatom (N or S) yields are higher from the chloro than from the bromo derivative, *ii*. on the contrary, bromine is required at the β position to nitrogen or sulfur to provide significant yields of the addition product, *iii*. azines give higher yields of the addition product than thiophene. If we now look at the reaction conditions, striking differences are observed depending on the nature of the solvents with substantial advantages of one method (A or B) over the other according to the nature of the reagent (Table 1, entries 3, 4, 12, 13). As a general trend, method A leads to higher yields from 2-chloro compounds (Table 1, entries 3, 4) whereas method B is more convenient with 3-bromo compounds (Table 1, entries 12, 13). These previously defined reaction conditions however are not very satisfactory notably with 2-halo substituted compounds as yields are lower than those previously obtained in the arylation of activated olefins.[9b]

The presence of the heteroatom in the ring can account for differences in efficiency between arylation and the heteroarylation reactions. Indeed the heteroatom in the substrate can compete with the weakly coordinating ligands like acetonitrile, pyridine or the activated olefin to form a new nickel species. Also, as compared to nitrogen, sulphur (entries 16-20) may exhibit a stronger affinity for nickel species leading possibly to fully coordinated unreactive nickel complexes. Finally, the consistent difference in reactivity when the halogen is located in position 2 as compared to position 3 can be rationalized by a stronger coordination of the corresponding adduct to nickel species in structure (I) than in (II) (Scheme 4) again leading to unreactive species.



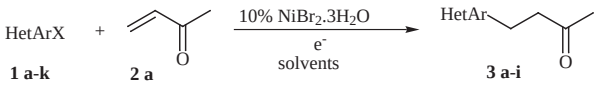
Scheme 4

On the basis of these assumptions we have been able to improve the yields by working at a higher temperature and in the presence of both excess of MVK (10 instead of 2.5 equiv) and the catalyst. The increase of the concentration of nickel species in the solution can be easily obtained from a stainless steel rod (Fe:Cr:Ni, 72:18:10) as the anode in place of the iron rod previously used. We thus can have a continuous release of nickel salts along with iron salts allowing for the maintenance of the minimum amount of efficient catalytic species over the electrolysis procedure. These new reaction conditions are defined in method C (Table 1) when the solvent is the DMF–pyridine, 9:1 and the reaction temperature is 75 °C.

As shown in Table 1, this procedure is the most suitable for α-chloroazines (entries 5, 8, 11) giving yields in the range of 80%. Slight improvement is also observed in the case of 2-chlorothiophene (Table 1, entry 19). In the case of 3-bromo substituted compounds there is no such an advantage in using method C as observed with 3-bromoquinoline (Table 1, entries 13-14).

We next focused on the application to heteroaryl halides bearing two or more heteroatoms in their ring such as diazines (pyrazyl and pyrimidyl chlorides), chlorobenzoxazole, and bromocafeine. The results are reported in Table 2. Activation of chloropyrazine **1l** by nickel catalyst and further reaction with MVK gives similar results from either method A or B (Table 2, entries 1, 2). We also found that the reaction of **1l** can be carried out in pure acetonitrile as solvent (procedure D), which is not appropriate for the standard arylation process, affording a substantial improvement of the yield (Table 2, entry 3).

Table 1 Nickel-Catalyzed Conjugate Addition Reaction of Pyridyl, Quinolyl, and Thienyl Halides to Methyl Vinyl Ketone (MVK)[a]



1 a-k **2 a** **3 a-i**

Entry	HeteroArX	MVK (equiv)	Method[b]	Reaction Time (h)	Product	Yield (%)
1	2-Bromopyridine **1a**	2.5	A	7	**3a**	30
2	**1a**	2.5	B	5	**3a**	16
3	2-Chloropyridine **1b**	2.5	A	6	**3a**	52
4	**1b**	2.5	B	8	**3a**	30
5	**1b**	10	C	7	**3a**	83
6	2-Chloro-5-CF_3-pyridine **1c**	2.5	B	6	**3b**	56
7	2-Chloro-6-MeO-pyridine **1d**	2.5–10	B	8	**3c**	18
8	**1d**	10	C	7	**3c**	72
9	3-Bromopyridine **1e**	2.5	B	3.5	**3d**	73
10	2-Chloroquinoline **1f**	2.5	A	5	**3e**	42
11	**1f**	10	C	3.5	**3e**	86
12	3-Bromoquinoline **1g**	2.5	A	8.5	**3f**	49
13	**1g**	2.5	B	4.1	**3f**	76
14	**1g**	10	C	3.5	**3f**	85
15	4-Chloro-2-Me-quinoline **1h**	2.7	B	4	**3g**	45
16	2-Bromothiophene **1i**	2.5	B	11	**3h**	15
17	**1i**	10	C	6	**3h**	0
18	2-Chlorothiophene **1j**	2.5	B	10	**3h**	10
19	**1j**	10	C	13	**3h**	31
20	3-Bromothiophene **1k**	2.5	B	8	**3i**	43

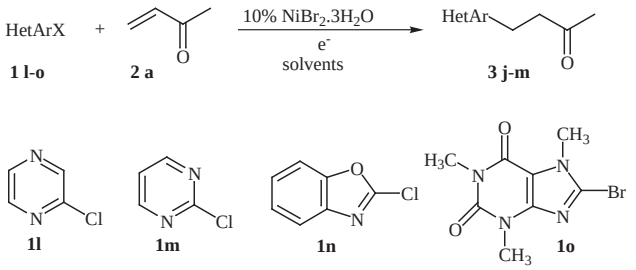
[a] Reactions conditions: heteroarylhalide (7 mmol), MVK (2.5–10 equiv), $NiBr_2{\cdot}3H_2O$ (0.1 equiv), I = 0.15 A.
[b] Method A: DMF−pyridine, 9:1, 60 °C, iron anode. Method B: DMF−MeCN (1:1), 60 °C, iron anode. Method C: DMF−pyridine, 9:1, 75 °C, stainless steel anode.

With 2-chloropyrimidine **1m** neither method A or B affords satisfactory results. We hypothesized that a highly efficient complexation of the catalyst by the heterocyclic reagent could hamper its reaction thus leading to a low turnover. Excess olefin (10 equiv) as well as a higher temperature (method C) did not afford significant improvement. However using acetonitrile as solvent as in the case of chloropyrazine **1l** enabled to get a satisfactory 53% yield. Excess of MVK was also necessary in the case of chlorobenzoxazole **1n** and 30% is the highest yield obtained in DMF–MeCN, 1:1 (method B) while no product was formed in DMF–pyridine, 9:1 (method C). Finally the conjugate addition reaction with 2-bromocafeine as substrate was possible at 80 °C in DMF–MeCN, 1:1 when the iron rod (entry 10, Table 2) was replaced by a stainless steel rod (entry 11, Table 2, method E).

Lastly, synthetic application of the standard method B was extended to other various electron deficient olefins (Table 3). For this study, we chose 3-bromoquinoline **1g**, a good substrate to alkylate (see entry 13, Table 1). The best results were obtained with mono-substituted olefins (methyl vinyl ketone, acrylonitrile, and ethyl acrylate). The conjugate addition reaction is less efficient with disubstituted olefins (entries 4−8, Table 3) even with dimethyl maleate and dimethyl fumarate which were good substrates in the arylation.[9a–b]

In conclusion the general method previously reported for arylation reaction[9a–b] of activated olefins can be applied to heteroaryl halides, though less efficiently, when conducted under standard reaction conditions (A or B). Reaction conditions have to be optimized for every type of structures since yields are closely dependent on the nature and number of heteroatoms in the ring and on the position of the halogen. Thus four experimental parameters can be tuned in the optimization experiments: the solvent, the olefin/heteroaryl halide ratio, the anode, and the temperature. 3-Heteroaryl halides mostly behave as aryl halides and can be reacted in typical reaction conditions referred to in method B. Because of the nickel affinity of the heteroatom in the aromatic nucleus and eventually of the functionalized chain, reaction conditions have been successfully redefined for the substrates containing nitrogen. This is clearly illustrated by the reactions of 2-haloheteroaryl compounds (Table 1) and 2-bromocafeine

Table 2 Extension to Nickel-Catalyzed Conjugate Addition Reaction of Substrates Containing Two or More Heteroatoms with MVK[a]



Entry	Hetero ArX	MVK (equiv)	Method[b]	Reaction time (h)	Product	Yield (%)
1	**1l**	2.5	A	5	**3j**	50
2	**1l**	2.5	B	5	**3j**	50
3	**1l**	2.5	D	5	**3j**	65
4	**1m**	2.5	A	10	**3k**	18
5	**1m**	2.5	B	6.5	**3k**	21
6	**1m**	10	C	4	**3k**	27
7	**1m**	10	D	6.5	**3k**	53
8	**1n**	10	B	6	**3l**	30
9	**1n**	10	C	3	**3l**	0
10[c]	**1o**	6−10	B	5.5	**3m**	Traces
11[c]	**1o**	10	E	3.5	**3m**	68

[a] Reactions conditions: heteroarylhalide (7 mmol), MVK (2.5−10 equiv), $NiBr_2 \cdot 3H_2O$ (0.1 equiv) I = 0.15 A.
[b] Method A: DMF−pyridine, 9:1, 60 °C, iron anode. Method B: DMF/MeCN, 1:1 at 60 °C, iron anode. Method C: DMF−pyridine 9:1, 75 °C, stainless steel anode. Method D: MeCN, 60 °C, iron anode, NBu_4BF_4 as supporting electrolyte. Method E: DMF−MeCN, 1:1, stainless steel anode.
[c] Reaction performed with 5 mmol of 2-bromocafeine at 80 °C.

(Table 2) with MVK, where a large excess of the activated olefin and constant supply of the catalyst precursor by anodic dissolution of a stainless steel anode can compensate the loss of the catalytic nickel species. The readily availability of the starting reagents and the simplicity of the procedure makes this methodology a convenient and straightforward way to provide new elaborated products of great importance, notably in bio-organic chemistry.

All reactions were carried out under argon atmosphere. All reagents unless indicated and supporting electrolytes were used as received without further purification. DMF and MeCN were dried over 3 Å molecular sieves and stored under argon. Melting point determinations were performed with a capillary melting point device (Electrothermal IA9100 Digital Melting Point Apparatus) and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 283B spectrophotometer. NMR spectra were obtained with Bruker AC 200 spectrometer (^1H at 200 MHz, ^{13}C NMR at 50.32 MHz). The mass spectra were measured (EI) with a gas chromatography coupled mass spectrometer at 70 eV (GCQ ThermoQuest) using a 30 m DB-5MS capillary column. Elemental analysis was determined by the Service Central d'Analyses (CNRS 69-Vernaison France) for novel compounds.

Nickel-Catalyzed Electroreductive Coupling; General Procedure

A single-compartment electrochemical cell[11] was equipped with a nickel grid (area 30 cm^2) as the cathode and a cylindrical iron or stainless steel rod (diameter 1 cm) as the anode. Under a slow stream of argon, tetrabutylammonium bromide (100 mg, 0.31 mmol) and tetrabutylammonium iodide (75 mg, 0.20 mmol) were dissolved as supporting electrolytes in a mixture of DMF (15 mL) and MeCN (15 mL) or DMF (27 mL) and pyridine (3 mL). 1,2-Dibromoethane (60 μL, 0.70 mmol) was added. A short electrolysis was performed at r.t. and at constant current density (0.5 A/dm^2) during 15 min. Then the current was turned off. The activated olefin (2.5 to 10 equiv), the heteroaryl halide (7.0 mmol), and nickel bromide hydrate (153 mg, 0.70 mmol) were successively added. The reaction mixture was then heated (60 °C−80 °C). The electrolysis was run at constant current density (0.5 A/dm^2). The reaction was monitored by GC and discontinued when most of the heteroaryl halide was consumed (3.5 to 11 h).

For compounds **3a**, **3b**, **3c, 3d**, **3e**, **3f**, **3k**, **3l**, **3o** the work-up was performed as follows: the reaction mixture was poured into sat. $NaHCO_3$ soln (100 mL) and the cell was rinsed with CH_2Cl_2 (30 mL). The resulting mixture was then extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were evaporated to dryness under reduced pressure. The residue was purified by silica-gel column chromatography to give the desired compound.

For compounds **3g**, **3h**, **3i**, **3n**, **3p**, **3q** the work-up was performed as follows: the reaction mixture was poured into Et_2O (100 mL), eventually decanted and filtered, and the cell was rinsed with HCl (1 N, 30 mL). The combined Et_2O solutions were then washed with HCl (1 N, 3 × 70 mL). The combined aqueous layers were neutralized and rendered basic by adding $NaHCO_3$ powder, filtered and extracted with Et_2O (4 × 70 mL). The combined extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by silica-gel column chromatography to give the desired compound.

For compounds **3m**, **3j** the work-up was performed as follows: The mixture was quenched with sat. NH_4Cl soln (60 mL) and extracted with EtOAc (3 × 70 mL for compound **3m**) or CH_2Cl_2 (3 × 70 mL for compound **3j**). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue thus obtained was purified by column chromatography to give desired compound.

4-(5-Trifluoromethylpyridin-2-yl)-butan-2-one (3b)

The residue was purified by column chromatography on silica-gel (70−230 mesh) with an increasing elution polarity (15 to 50%, Et_2O−pentane) to afford 0.87g (56%) of **3b** as a colorless liquid.

Anal. Calcd for $C_{10}H_{10}F_3NO$: C, 55.30; H, 4.64; N, 6.45. Found: C, 54.95; H, 4.76; N, 6.28.

4-(6-Methoxypyridin-2-yl)-butan-2-one (3c)

The residue was purified by column chromatography on silica-gel (70–230 mesh) with a mixture of pentane−CH_2Cl_2,1:1 as eluent to give 0.902 g (72%) of **3c** as a colorless liquid .

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.74; H, 7.36, N, 7.81.

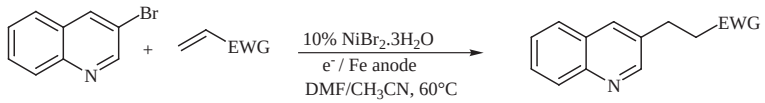
4-Quinolin-2-yl-butan-2-one (3e)

The residue was purified by column chromatography on silica-gel (70–230 mesh) with a mixture of EtOAc−pentane, 2:1 as eluent to give 1.20 g (86%) of **3e** as a colorless liquid.

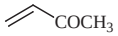
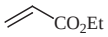
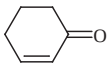
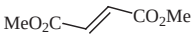
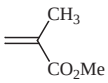
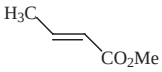
4-Quinolin-3-yl-butan-2-one (3f)

The solid residue was purified by column chromatography on silica-gel (230–400 mesh) with a mixture of EtOAc−pentane, 2:1 as eluent to give 1.18 g (85%) of **3f** as shiny white crystals.

Table 3 Reaction of 3-Bromoquinoline (**1g**) with Various Activated Olefins according to Method B[a]



1g (7 mmol) **2a-h** (2.5 equiv) **3f, 3n-s**

Entry	Olefin	Reaction Time (h)	Product	Yield (%)
1	 **2a**	3.7	**3f**	76
2	 **2b**	4.25	**3n**	44
3	 **2c**	4.5	**3o**	51
4	 **2d**	4	**3p**	25
5	 **2e**	7	**3q**	16
6	 **2f**	8	**3q**	18
7	 **2g**	4.5	**3r**	5
8	 **2h**	5	**3s**	5

[a] Reactions conditions: 3-bromoquinoline (7 mmol), activated olefin (2.5 equiv), $NiBr_2 \cdot 3H_2O$ (0.1 equiv), I = 0.15 A, DMF−MeCN, 1:1, 60 °C, iron anode.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.37; H, 6.58; N, 7.03. Found: C, 78.47; H, 6.58; N, 7.16.

4-(2-Methylquinolin)-4-yl-butan-2-one (3g)
The solid residue was purified by flash chromatography (silica-gel, 230–400 mesh, eluent EtOAc−pentane, 2:1) to give 0.67g (45%) of **3g** as shiny white crystals.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.53; H, 7.02; N, 6.59.

4-Pyrazin-2-yl-butan-2-one (3j)
The compound was purified by column chromatography on silica-gel (70–230 mesh) with 2% MeOH in Et_2O as eluent to give 0.68 g (65%) of **3j** as a colorless liquid.

4-Pyrimidin-2-yl-butan-2-one (3k)
The residue was purified by column chromatography on silica-gel (70–230 mesh, eluent: CH_2Cl_2) to give 0.55 g (53%) of slightly pale liquid **3k** which tends to darken over time.

2(3-Oxobutyl)benzoxazole (3l)
The solid residue was purified by column chromatography on silica-gel (230–400 mesh) with an increasing elution polarity (10% to 30%, EtOAc−pentane) to afford 0.40g (30%) of **3l** as white crystals.

Anal. Calcd for $C_{11}H_{11}O_2N$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.77; H, 5.96; N, 7.40

3-Oxobutylcafeine (3m)
The solid residue was purified by column chromatography on silica-gel (70–230 mesh) with 1% MeOH−CH_2Cl_2 as eluent to give 1.35 g (68%) of **3m** as white crystals.

3-Quinolin-3-yl-propanenitrile (3o)
The residue was purified by column chromatography on silica-gel erased (230–400 mesh) silica using EtOAc−pentane, 1:1 as eluent to give 0.65 g (51%) of **3o** as a colorless liquid.

Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 78.91; H, 5.52; N, 15.27.

3-Quinolin-3-yl-cyclohexanone (3p)
The compound was purified by column chromatography on silica-gel (70–230 mesh) with 0.5% MeOH−CH_2Cl_2 as eluent to give 0.40 g (25%) of **3p** as a colorless liquid.

Dimethyl α-(quinolin-3-yl)-succinate (3q)
The residue was purified by column chromatography on silica (70–230 mesh) with 0.5% MeOH−CH_2Cl_2 as eluent to give 0.35 g (18%) of **3q** as a solid (from dimethylfumarate)

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.11; H, 5 49; N, 4.89.

Spectral data are given in Table 4.

The following products were identified by comparison of their spectral data with those given in literature: 4-pyridin-2-yl-butan-2-one,[12] 4-pyridin-3-yl-butan-2-one,[13] 4-thiophene-2-yl-butan-2-one,[14] 4-thiophen-3-yl-butan-2-one,[14] ethyl 3-quinolin-3-yl-propanoate.[15]

Table 4. Physical and Spectroscopic Data of Compounds **3b**−**q**

Product	Mp (°C)	IR (NaCl) (cm^{-1})	^{1}H NMR (200 MHz, $CDCl_3$) ppm, *J* (Hz)	^{13}C NMR (50.32 MHz, $CDCl_3$), ppm	MS, *m*/*z* (%)
3b	liquid	1720, 1610, 1575	8.79 (s, 1 H), 7.84 (dd, 1 H, *J* = 7.3, 2.2), 7.37 (d, 1 H, *J* = 8.1), 3.17 (t, 2 H, *J* = 6.5), 3.03 (t, 2 H, *J* = 6.5), 2.23 (s, 3 H)	207.1, 164.4, 145.9, 145.8 133.2, 133.1, 122.9, 41.4 31.3, 29.3	218 (base peak), 202, 174
3c	liquid	3030, 1720, 1590	7.37 (t, 1 H, *J* = 7.7), 6.65 (d, 1 H, *J* = 7.7), 6.46 (d, 1 H, *J* = 7.7), 3.61 (s, 3 H), 2.87 (m 4 H), 2.12 (s, 3 H)	208.1, 163.5, 157.9, 138.7 115.2, 107.6, 53.0, 42.0 31.3, 29.8	180 (base peak)
3e	liquid	3030, 1720, 1600, 1560, 1500	7.87 (d, 1 H, *J* = 8.3), 7.86 (d, 1 H, *J* = 8.4), 7.60 (d, 1 H, *J* = 8.3), 7.52 (td, 1 H, *J* = 7.5, 1.2), 7.31(t, 1 H, *J* = 7.5), 7.13 (d, 1 H, *J* = 8.4), 3 11(t, 2 H, *J* = 7.0), 2.90 (t, 2 H, *J* = 7.0), 2.08 (s, 3 H)	207.6, 160.5, 147.4 135.9, 129.0, 128.4 127.2, 126.5, 125.5, 121.4, 41.5, 32.1, 29.9	200, 184, 156 (base peak), 128
3f	75	3030, 1710, 1600, 1570, 1490	8.66 (s, 1 H), 7.94 (d, 1 H, *J* = 8.3), 7.82 (s, 1 H), 7.63 (d, 1 H, *J* = 7.6), 7.54 (td, 1 H, *J* = 7.6 1.4), 7.39 (t, 1 H, *J* = 7.6), 2 96 (t, 2 H, *J* = 7.2), 2.75 (t, 2 H, *J* = 7.2), 2.04 (s, 3 H)	206.8, 151.7, 146.8, 134.3, 133.7, 129.0, 128.7, 127.9, 127.3 126.6, 44.2, 29.9, 26.7	199 184 (base peak) 156, 142, 129, 115
3g	92	3040, 1720, 1605, 1565, 1515	8.11 (m, 1 H), 8.02 (m, 1 H), 7.75 (td, 1 H, *J* = 7.6, 1.2), 7.58 (td, 1 H, *J* = 7.6, 1.2), 7.22 (s, 1 H), 3.40 (t, 2 H, *J* = 7.6), 2.97 (t, 2 H, *J* = 7.6), 2.78 (s, 3 H), 2.26 (s, 3 H)	206.8, 158.6, 147.9, 146.7, 129.4, 129.1, 125.6, 125.4, 122.9, 121.5, 43.2, 29.9, 25.5, 25.2	213, 170 (base peak)
3j	liquid		8.30–8.43 (m, 3 H), 2.93 (m, 4 H), 2.10 (s, 3 H)	207.0, 156.0, 144.8 143.7, 142.1, 41.2, 29.8 28.5	151, 135, 107 (base peak)
3k	liquid	3060, 1720, 1580, 1440	8.56 (d, 2 H, *J* = 4.9), 7.05 (t, 1 H, *J* = 4.9), 3.20 (t, 2 H, *J* = 6.9), 2.94 (t, 2 H, *J* = 6.9), 2.16 (s, 3 H)	207.1, 169.2, 156.5, 118.1, 40.1, 32.4, 29.5	151, 135, 107 (base peak)
3l	89		7.56 (m, 1 H), 7.38 (m, 1 H), 7.20 (m, 2 H), 3.06 (m, 4 H), 2.16 (s, 3 H)	205.8, 165.9, 150.6, 141.0, 124.4, 124.0, 119.2, 110.1, 39.2, 29.6, 22.2	191 (base peak), 146
3m	141		3.88 (s, 3 H), 3.44 (s, 3 H), 3.29 (s, 3 H), 2.92 (m, 4 H), 2.16 (s, 3 H)	206.7, 155.2, 153.1, 151.7, 147.8, 107.4, 39.7, 31.6, 30.0, 29.7, 27.8, 23.8	264, 221 (base peak)
3o	liquid	2250, 1605, 1570, 1490	8.65 (d, 1 H, *J* = 1.8), 7.94 (d, 1 H, *J* = 8.4), 7.88 (d, 1 H, *J* = 1.8), 7.65 (dd, 1 H, *J* = 8.2, 1.2), 7.56 (td, 1 H, *J* = 7.6, 1.3), 7.40 (td, 1 H, *J* = 7.6, 1.3), 2.99 (t, 2 H, *J* = 7.3), 2.58 (t, 2 H, *J* = 7.3)	150.9, 147.2, 134.7, 130.7, 129.3, 129.1, 127.7, 127.6, 126.9, 118.8, 28.6, 18.8	182, 142 (base peak), 115
3p	liquid	1740, 1625, 1590, 1520	8.74 (d, 1 H, *J* = 2.2), 8.00 (d, 1 H, *J* = 8.4), 7.86 (d, 1 H, *J* = 2.2), 7.71 (m, 1 H), 7.61 (m, 1 H), 7.46 (m, 1 H), 3.16 (br m, 1 H), 2.61 (m, 2 H), 2.41 (m, 2 H), 2.09 (m, 2 H), 1.89 (m, 2 H)	209.9, 150.4, 147.1, 136.8, 132.5, 129.1, 129.0, 128.0, 127.6, 126.9, 48.1, 42.1, 41.0, 32.3, 25.2	226, 197, 182, 168 (base peak), 154, 140
3q	67	3020, 1750, 1605, 1575, 1500	8.80 (s, 1 H), 8.05–7.99 (m, 2 H), 7.73 (dd, 1 H, *J* = 8.1, 1.5), 7.65 (td, 1 H, *J* = 7.4, 1.5), 7.49 (td, 1 H, *J* = 7.4, 1.5), 4.26 (dd, 1 H, *J* = 9.4, 5.9), 3.64 (s, 3 H), 3.61 (s, 3 H), 3.27 (dd, 1 H, *J* = 17.0, 9.4), 2.75 (dd, 1 H, *J* = 17.0, 5.9)	172.6, 171.4, 150.5, 147.5, 134.3, 134.2, 130.5, 129.6, 129.2, 127.7, 127.0, 52.6, 52.0, 44.7, 37.1	274, 273, 241 213 (base peak), 198, 183, 172, 154, 140, 128

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