Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 711

www.rsc.org/obc

PAPER

Oxidoreductive coupling of thiols with aryl halides catalyzed by copper on iron†

Szabolcs Kovács and Zoltán Novák*

Received 7th July 2010, Accepted 1st October 2010
DOI: 10.1039/c0ob00397b

Synthesis and utilization of a simple copper on iron catalyst in the coupling of aryl halides with thiols through disulfide intermediate is reported. The iron support of copper catalyst ensures reductive media for the coupling, allows easy removal of the metals by outer magnetic field and enables the recycling of the catalyst.

Introduction

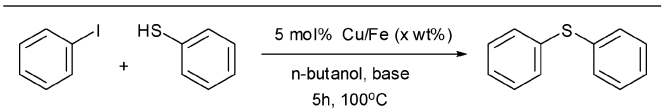
The transition metal catalyzed carbon-sulfur bond forming reaction represents an important tool for the practical synthesis of sulfides from aryl halides and sulfur sources.[1] Aryl sulfides have significant relevance from clinical interests and biological, pharmaceutical aspects.[2] Since the initial report of Migita and coworkers[3] on the palladium catalyzed carbon-sulfur bond forming reaction,[4] several improvements have been achieved for the development of more efficient, beneficial and environmentally friendly conditions for the aromatic thiolation. In this context, different transition metals such as indium,[5] copper[6] and iron[7] have proved to be applicable catalysts under ligand free conditions,[8] in aqueous media[7b] or with utilization of solid supported catalysts.[9]

The major problem with the transition metal catalyzed thiolation reaction is the inevitable formation of disulfide side product through the facile oxidation of thiols. Reductive coupling of disulfides instead of thiols with aryl halides serves an elegant solution to the problem. The concept has been formulated by Srogl *et al.*[10] and demonstrated by Li *et al.*[11] very recently. These conditions work efficiently with disulfides and the application of reductive reaction media ensures the coupling of easily accessible thiols and aryl halides without the production of disulfide side product.

Results and discussion

For the construction of new carbon-sulfur bonds in aromatic molecules we intended to develop reusable copper on iron heterogeneous catalysts. Exploiting the differences of standard reduction potentials of copper(II)/copper(0) and Fe(II)/Fe(0) systems, copper can be spontaneously deposited onto the surface of iron in a simple single metal replacement reaction. The formed copper on iron bimetallic system supposedly would be applicable in several copper catalyzed transformations, and the iron-supported copper can be easily separated using outer magnetic field after the reaction. Moreover, iron serves not only as the supporter of the copper catalyst, but ensures the reductive media for the carbon-sulfur bond forming reaction. The presence of reducing agent presumably lowers the amount of disulfide byproducts in the reaction mixture.

Table 1 Comparison of copper on iron catalysts[a]



Entry	Catalyst	Base	Conversion (%)[b]	Sulfide : disulfide[b]
1	Fe	K_2CO_3	0	0
2	Cu powder	K_2CO_3	80[c]	7 : 1
3	0.5 wt% Cu/Fe	K_2CO_3	82	14 : 1
4	1 wt% Cu/Fe	K_2CO_3	89	32 : 1
5	2 wt% Cu/Fe	K_2CO_3	92	38 : 1
6	5 wt% Cu/Fe	K_2CO_3	93	69 : 1
7	5 wt% Cu/Fe	KOH	94	22 : 1
8	5 wt% Cu/Fe	K_3PO_4	97	>100 : 1
9	5 wt% Cu/Fe	DIPEA	68	59 : 1

[a] Reaction conditions: 0.5 mmol iodobenzene, 0.5 mmol thiophenol, 0.55 mmol K_2CO_3, 0.1 mL n-butanol, 5 mol % Cu/Fe, 100 °C. [b] Conversions and sulfide : disulfide ratios were determined by GC. [c] Conversion after 7 h.

Whereas iron itself was not able to catalyze the coupling of iodobenzene and thiophenol in butanol at 100 °C (Table 1, entry 1), copper powder proved to be an applicable catalyst for the thiolation (entry 2). However, the presence of copper alone caused the formation of significant amount of disulfide during the reaction (7 : 1 sulfide : disulfide ratio). For further examination of the aromatic thiolation we synthesized several Cu/Fe catalyst with different composition (0.5, 1, 2 and 5 wt% copper content) from iron powder (99% purity, ~200 μm particle size) and copper(II) sulfate in deoxygenated water at 25 °C. We compared the catalytic

Department of Organic Chemistry, Institute of Chemistry, Eötvös Loránd University, Pázmány Péter stny. 1/a, Budapest, Hungary. E-mail: novakz@elte.hu; Fax: +36-1-372-2909; Tel: +36-1-372-2500 ext. 1610

† Electronic supplementary information (ESI) available: Results of the optimization studies, experimental procedures and ^1H and ^{13}C NMR spectra of the new products. See DOI: 10.1039/c0ob00397b

activities of the prepared Cu/Fe heterogeneous catalysts in the coupling of iodobenzene and thiophenol in butanol at 100 °C under air. The iron supported copper catalysts were found to be effective for the thiolation. Increasing the copper content of the Cu/Fe catalysts, we obtained better conversions (entries 3–6). More importantly the amount of disulfide byproduct decreased significantly (entry 6) when the copper content of the catalyst increased, and the application of 5 wt% Cu/Fe catalyst almost completely suppressed the formation of the disulfide side product. After finding an optimal catalyst composition, next we examined the base effect on the coupling. The results revealed that inorganic bases such as K_2CO_3, KOH, and K_3PO_4 are slightly better bases than organic diisopropylethylamine (entries 8–10).

After finding applicable bases we examined the solvent effect on the coupling of thiophenol and iodobenzene (Fig. 1). In the presence of K_2CO_3 we compared several solvents and we found that the application of polar media is preferable for the thiolation. Although, the reaction took place with similar efficiency in butanol, DMF, dioxane and DMSO, full conversion was reached when DMA/K_2CO_3 solvent-base pair was used. Interestingly, in case of DMA solvent the time conversion plot did not show saturation profile, compared to the other applied polar solvents.

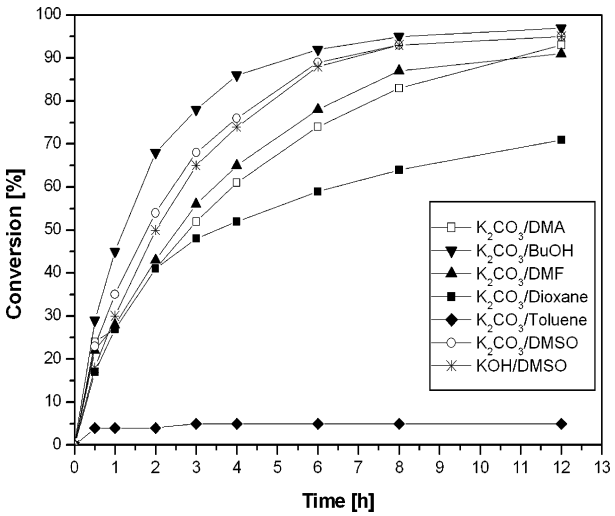


Fig. 1 Examination of the solvent effect. Reaction conditions: 0.5 mmol iodobenzene with 0.5 mmol thiophenol, 5 mol% Cu/Fe (1 wt%), 0.55 mmol base in 0.5 mL Solvent. 100 °C.

During the examination of the solvent effect we observed the presence of large amount of disulfide in the reaction mixture at the early stage of the reaction during the coupling of iodobenzene and thiophenol.

Next, we examined the changes of the amount of disulfide side product during the Cu/Fe catalyzed coupling reactions. We have observed the rapid formation of diphenyl-disulfide from thiophenol in DMA at 110 °C (Fig. 2)[12] at the beginning of the reaction. Following the oxidation of thiol, the disulfide slowly decomposes supposedly with the aid of the iron support. After the appropriate period of time, the intermediate was completely consumed *via* reductive cleavage and subsequent coupling.

When lower amounts of copper catalyst (2.5 mol% instead of 5 mol%) was used at 110 °C the reaction was slower and byproduct disulfide was present in higher amount at the beginning

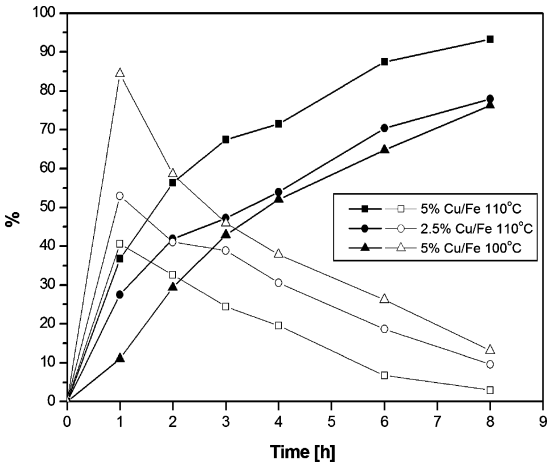


Fig. 2 (■●▲): Conversions of iodobenzene to diphenylsulfide. (□○△): Change of disulfide/(sulfide+disulfide) ratio (%). Reaction conditions: 0.5 mmol iodobenzene with 0.5 mmol thiophenol, Cu/Fe (1 wt%), 0.55 mmol K_2CO_3 in 0.5 mL DMA.

of the reaction. Reaction at 100 °C in the presence of 5 mol% Cu/Fe (1 wt% catalyst) showed lower conversions and the disulfide formation was twice as it was found in case of the reaction performed at 110 °C.

Similarly to Li and co-workers's findings,[11] reaction of diphenyl disulfide with iodobenzene in the presence of 5% Cu/Fe (1 wt% Cu) in DMA at 110 °C gave the desired diphenylsulfide. These results showed that disulfide is an intermediate during the thiolation process, and the used copper on iron both acts as reducing agent and catalyst during the transformation.

To explore the scope of the reaction we performed the coupling reactions of structurally and electronically diverse aryl iodides and thiols with copper on iron catalysts in DMA at 100 °C. Diphenyl sulfide **3a** was prepared with 91% yield after the reaction (Table 2, entry 1). The presence of electron donating methyl or methoxy groups on the phenyl rings both in the thiol and the aryl iodide did not cause significant changes in the conversions (entries 2–3). Coupling of *o*-methyl- and aminothiophenol with iodobenzene also afforded the appropriate sulfides **3e** and **3f** with high yields. Sterically more hindered substrates such as 2-isopropyliodobenzene and 1-iodonaphthalene were also proved to be excellent substrates for the copper on iron catalyzed coupling, and the coupled products were isolated with good yields (entries 7 and 8). Introduction of the naphthalene into the sulfide **3i** was also achieved with 2-naphthalenethiol. Coupling of thiophenol and 1-bromo-4-iodobenzene gave product **3j** selectively, demonstrating the higher reactivity of iodide over bromide. Aryl iodides with electron withdrawing groups such as cyano and acetyl group were successfully coupled with sterically hindered 2, 6-dimethylthiophenol (entries 11 and 12). Although alkyl-aryl sulfide **3m** was prepared from iodobenzene and dodecanethiol, the yield was lower than those of the diaryl sulfides. Syntheses of aryl-hetaryl sulfides were also achieved with the catalyst. But coupling of 2-mercaptopyridine with iodobenzene gave lower yield (entry 14, 59%) than that of the coupling of 2-iodopyridine and thiophenol (entry 14, 92%).

However, regioisomers 2 and 3-iodopyridine were coupled with same efficiency (entry 14 and 15). Other heterocyclic structures

Table 2 Cu/Fe catalyzed coupling of aryl halides with thiols[a]

ArI + ArSH $\xrightarrow[K_2CO_3,\ DMA,\ 100\ °C]{5\ mol\%\ Cu/Fe\ (5\ wt\%)}$ ArSAr

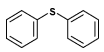
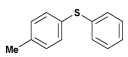
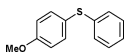
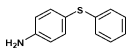
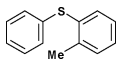
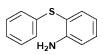
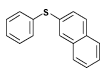
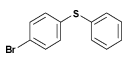
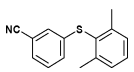
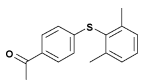
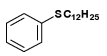
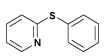
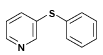
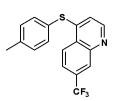
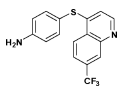
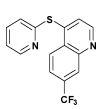
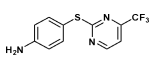
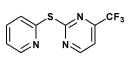
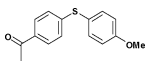
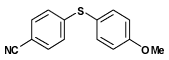
Entry	Product		Time/h	Yield (%)[b]
1		**3a**	8	91
2		**3b**	8	95; 91[c]
3		**3c**	8	93; 95[d]
4		**3d**	8	86
5		**3e**	8	97
6		**3f**	8	85
7		**3g**	8	93
8		**3h**	8	88
9		**3i**	8	81
10		**3j**	8	78
11		**3k**	8	95
12		**3l**	8	84
13		**3m**	8	43
14		**3n**	8	92; 59[e]
15		**3o**	8	94
16		**3p**	16	58
17		**3q**	16	87
18		**3r**	24	69
19		**3s**	24	62
20		**3t**	24	80

Table 2 *(Contd.)*

ArI + ArSH $\xrightarrow[K_2CO_3,\ DMA,\ 100\ °C]{5\ mol\%\ Cu/Fe\ (5\ wt\%)}$ ArSAr

Entry	Product		Time/h	Yield (%)[b]
21		**3u**	16,[f] 24[g]	82,[f] 85[g]
22		**3v**	16,[f] 48[g]	91,[f] 98[g]

[a] Reaction conditions: 0.5 mmol aryl halide, 0.5 mmol thiol, 0.55 mmol K_2CO_3, 0.1 mL DMA, 5 mol % Cu/Fe (5 wt%). [b] Yields of isolated product after chromatographic purification. [c] reaction of 4-methylthiophenol and iodobenzene, [d] reaction of 4-methoxythiophenol and iodobenzene. [e] reaction of 2-mercaptopyridine and iodobenzene. [f] reaction of aryl bromide. [g] reaction of aryl chloride.

such as electron deficient quinoline and pyrimidine bearing thiol functional group were effectively coupled with aromatic and heteroaromatic iodides with good yields (entries 16–20). Besides aromatic iodides, electron deficient bromides and chlorides were successfully coupled with 4-methoxythiophenol in the presence of Cu/Fe catalysts with good yields. Longer reaction time (16 h for bromides, 24–48 h for chlorides) was necessary for the completion of the reaction (entries 21 and 22).

Finally, we examined the possible recycling of the catalyst after its use in the coupling of thiophenol and iodobenzene in DMA at 100 °C. The separation of the copper on iron catalyst from the reaction mixture can be easily achieved using outer magnetic field. After the removal of the reaction mixture, the catalyst was washed and dried, then reused several times under the same conditions. We have found that the catalyst could be used three times without the lost of activity (full conversions were obtained in 8 h). In the fourth and the fifth cycle we observed 98% and 80% conversions, respectively. These data demonstrate small activity lost of the catalyst during the recycling process.

Conclusions

In conclusion, we have prepared and successfully applied simple and easily accessible copper on iron catalysts for the thiolation of aromatic halides. Regarding the mechanistic steps we observed the fast oxidation of the thiol at the beginning of the reaction, and we found that the presence of iron ensures reductive media for the straightforward formation of the desired sulfides through the reductive cleavage of the disulfide intermediate. The developed conditions for the coupling of thiols based on the properties of copper on iron catalysts offers effective, economic and environmentally benign synthetic tool for the preparation of organic sulfides on broad scale without the application of inert atmosphere. Moreover, the reusable copper on iron catalysts can be easily separated from the reaction mixture during the workup with the aid of external magnetic field.

Experimental

General

Unless otherwise indicated, all starting materials were obtained from commercial suppliers, and were used without further

purification. Analytical thin-layer chromatography (TLC) was performed on Merck DC pre coated TLC plates with 0.25 mm Kieselgel 60 F254. Visualization was performed with a 254 nm UV lamp. The 1H and ^{13}C-NMR spectra were recorded on a Bruker Avance-250 spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for 1H, δ 77.0 for ^{13}C). Coupling constants (J) are reported in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet). Combination gas chromatography and low resolution mass spectrometry was obtained on an Agilent 6890 N Gas Chromatograph (30 m × 0.25 mm column with 0.25 μm HP-5MS coating, He carrier gas) and Agilent 5973 Mass Spectrometer (Ion source: EI+, 70 eV, 230 °C; interface: 300 °C). IR spectra were obtained on a Bruker IFS55 spectrometer on a single-reflection diamond ATR unit. All melting points were measured on Büchi 501 apparatus and are uncorrected. High-resolution mass spectra were recorded on an Agilent Technologies 6210 Time of Flight mass spectrometer.

Preparation of copper on iron catalyst

To a round-bottom flask was charged with iron powder (5 g, 89.5 mmol, 99% purity, ~200 μm particle size) and water (de-oxygenated with argon) (50 mL). The aqueous solution of $CuSO_4$ (125.6 mg, 0.79 mmol) (50 ml) was dropped in the mixture under argon atmosphere over 1 h and stirred with mechanical-stirrer vigorously for 3 h. The catalyst was separated with magnet and washed with deoxygenated water (5 × 20 mL) than acetone (3 × 20 mL) and dried under reduced pressure.

General procedure for the synthesis of sulfides

A mixture of aryl halide (0.5 mmol, 1 eq.), thiol (0.5 mmol, 1 eq.), 5 mol% Cu/Fe (5 wt%) (32 mg, 0.025 mmol Cu), K_2CO_3 (76 mg, 0.55 mmol, 1.1 eq), and DMA (100 μL) were heated for 8–48 h at 100 °C. After allowing the mixture to cool to room temperature, the mixture was diluted with ethyl acetate (5 mL). The catalyst was separated with magnet and washed with ethyl acetate (2 × 5 mL) and with water (2 × 5 mL). The organic phase was separated and dried with Na_2SO_4, filtered, and the solvent was removed under vacuum, and the residue was purified by chromatography on silica gel to give desired aryl sulfide.

Diphenylsulfide (3a)[13]. General procedure was followed (8 h), colourless oil, 85 mg (0.46 mmol, 91% yield), R_f (hexane) = 0.80; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.29–7.12 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 135.8, 131.0, 129.2, 127.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 186 (100, [M$^+$]), 152(14), 92(12), 77(20), 51(36).

Phenyl-*p*-tolylsulfide (3b)[13]. General procedure was followed (8 h), colourless oil, 95 mg (0.47 mmol, 95% yield from the reaction of iodotoluene and thiophenol), 91 mg (0.45 mmol, 91% yield from the reaction of iodobenzene and 4-methylthiophenol), R_f (hexane) = 0.50; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.25–7.04 (m, 9H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 137.6, 137.1, 132.2, 131.3, 130.0,129.8, 129.0, 126.4; MS (EI, 70 eV) m/z (% relative intensity, ion): 200 (100, [M$^+$]), 184(40), 91(36).

4-Methoxyphenyl-phenylsulfide (3c)[13]. General procedure was followed (8 h), slightly yellow oil, 101 mg (0.47 mmol, 93% yield from the reaction of 4-iodoanisole and thiophenol), 103 mg (0.48 mmol, 95% yield from the reaction of iodobenzene and 4-methoxythiophenol), R_f (hexane: EtOAc 10 : 1) = 0.66; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.33 (d, J = 8.8 Hz, 2H), 7.18–7.00 (m, 5H), 8.80 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 159.7, 138.5, 135.3, 128.8, 128,1,125,7, 124.2, 114.9; MS (EI, 70 eV) m/z (% relative intensity, ion): 216 (100, [M$^+$]), 201(62), 171(18), 129(22), 77(19), 51(18).

4-Aminophenyl-phenylsulfide (3d)[14]. General procedure was followed (8 h), white solid, 87 mg (0.43 mmol, 86% yield), mp.: 91 °C lit.: 90.0 °C. R_f (hexane: EtOAc 6 : 4) = 0.65; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.22 (d, J = 8.5 Hz, 2H), 7.16–6.98 (m, 5H), 6.59 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 146.7, 139.6, 136.0, 128.8, 127.4, 125.2, 120.7, 115.9; MS (EI, 70 eV) m/z (% relative intensity, ion): 201 (100, [M$^+$]), 169(25), 124(28).

Phenyl-*o*-tolylsulfide (3e)[13]. General procedure was followed (8 h), colourless oil, 97 mg (0.48 mmol, 97% yield), R_f (hexane) = 0.55; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.21–6.99 (m, 9H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 139.9, 136.1, 133.7, 132.9, 130.5, 129.6, 129.1, 127.8, 126.7, 126.3; MS (EI, 70 eV) m/z (% relative intensity, ion): 200 (100, [M$^+$]), 185(23), 165(21), 121(42), 91(41), 65(29), 51(25).

2-Aminophenyl-phenylsulfide (3f)[15]. General procedure was followed (8 h), colourless solid, 85 mg (0.42 mmol, 85% yield); mp.: 40 °C, lit.: 42 °C, R_f (hexane: EtOAc 8 : 2) = 0.66; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.35 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz 1H), 7.16–7.07 (m, 3H), 7.02–6.95 (m, 3H) 6.65–6.61 (m, 2H), 4.14 (bs, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 148.7, 137.4, 136.7, 131.0, 128.9, 126.3, 125.3, 118.7, 115.3, 114.2; MS (EI, 70 eV) m/z (% relative intensity, ion): 201 (100, [M$^+$]), 186(15), 167(25), 80(16).

2-Isopropylphenyl-phenylsulfide(3g)[4e]. General procedure was followed (8 h), colourless oil, 106 mg (0.46 mmol, 93% yield), R_f (hexane) = 0.57; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.27–6.98 (m, 9H), 3.47 (hept, J = 6.8 Hz, 1H), 1.12 (s, 3H), 1,10 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 150.9, 137.8, 134.4, 133.0 129.8, 129.5, 128.9, 127.1, 126.57, 126.54, 31.1, 24.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 228 (100, [M$^+$]), 211(97), 135(72), 91(64), 71(33).

Naphthalen-1-yl-phenylsulfide (3h)[4e]. General procedure was followed (8 h), colourless oil, 104 mg (0.44 mmol, 88% yield), R_f (hexane) = 0.48; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8.30–8.23 (m, 1H), 7.74–7.67 (m, 2H), 7.53 (dd, J_1 = 7.3 Hz, J_2 = 1.1 Hz, 1H), 7.39–7.32 (m, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.06–6.96 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 136.8, 134.1, 133.5, 132.5, 131.1, 129.1, 129.0, 128.9, 128.5, 126.9, 126.4, 126.0, 125.7, 125.5; MS (EI, 70 eV) m/z (% relative intensity, ion): 236 (100, [M$^+$]), 202(22), 115(37).

Naphthalen-2-yl-phenylsulfide (3i)[16]. General procedure was followed (8 h), white solid, 103 mg (0.44 mmol, 87% yield); mp.: 46 °C, lit.: 49–50 °C, R_f (hexane) = 0.44; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.71 (s, 1H), 7.66–7.56 (m, 3H), 7.33–7.23 (m, 5H), 7.20–7.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 135.8, 133.7, 132.9, 132.2, 130.8, 129.8, 129.2, 128.8, 128.7, 127.7, 127.3, 127.0, 126.5, 126.1; MS (EI, 70 eV) m/z (% relative intensity, ion): 236 (100, [M$^+$]), 202(18), 115(34).

4-Bromophenyl-phenylsulfide (3j)[17]. General procedure was followed (8 h), colourless oil, 104 mg (0.39 mmol, 78% yield), R_f (hexane) = 0.70; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.31–7.15 (m, 7H), 7.05 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 135.4, 134.7, 132.1, 132.0, 131.5, 129.3, 127.5, 120.8; MS (EI, 70 eV) m/z (% relative intensity, ion): 266 (65, [M$^+$]), 184(100), 152(32), 108(27), 92(26), 51(26).

3-(2,6-Dimethylphenylthio)-benzonitrile (3k). General procedure was followed (8 h), white solid, 114 mg (0.48 mmol, 95% yield); mp.: 77–78 °C, R_f (hexane : EtOAc 10 : 1) = 0.59; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.26–7.04 (m, 6H), 6.98 (s, 1H), 2.3 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 143.7, 140.4, 130.0, 129.5, 129.3, 128.7, 128.4, 128.0, 118.4, 113.0, 21.6; MS (EI, 70 eV) m/z (% relative intensity, ion): 239(100, [M$^+$]), 206(25), 190(18), 136(38), 105(41), 77(54). IR (ATR) 2225, 1561, 1460, 1399, 1378, 1194, 874, 798, 776, 681 cm^{-1}, HRMS calcd for $C_{15}H_{14}NS$ [M+H]$^+$ 240.0841, found 240.0843.

4-(2,6-Dimethylphenylthio)-benzophenone (3l). General procedure was followed (8 h), slightly yellow solid, 108 mg (0.42 mmol, 84% yield), mp.: 91–92 °C, R_f (hexane : EtOAc 8 : 2) = 0.65; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.66 (dt, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 2H), 7.21–7.08 (m, 3H), 6.85 (dt, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 2H), 2.41 (s, 3H), 2.30 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 196.9, 145.2, 143.8, 133.4, 129.8, 128.82, 128.76, 128.6, 124.6, 26.2, 21.6; MS (EI, 70 eV) m/z (% relative intensity, ion): 256 (59, [M$^+$]), 241(100), 198(27), 77(26). IR (ATR) 1676, 1584, 1355, 1259, 1106, 959, 819, 782, 620, 588 cm^{-1}, HRMS calcd for $C_{16}H_{17}OS$ [M+H]$^+$ 257.0995, found 257.0993.

Dodecyl-phenylsulfide (3m)[4h]. General procedure was followed (8 h), white solid, 60 mg (0.22 mmol, 43% yield); mp.: 31–32 °C, lit.: 33–34 °C, R_f (hexane) = 0.45; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.26–7.16 (m, 4H), 7.11–7.05 (m, 1H), 2.83 (t, J = 7.4 Hz, 2H), 1.57 (m, 2H), 1.18 (m, 18H), 0.81 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 137.0, 128.75, 128.74, 33.5, 31.9, 29.69, 29.63, 29.57, 29.49, 29.33, 29.15, 29.11, 28.8, 22.7, 14.1; MS (EI, 70 eV) m/z (% relative intensity, ion): 278 (13, [M$^+$]), 123(21), 110(100), 55(16).

2-Phenylthio-pyridine (3n)[14]. General procedure was followed (8 h), colourless oil, 86 mg (0.46 mmol, 92% yield from the reaction of 2-iodopyridine and thiophenol), 55 mg (0.29 mmol, 59% yield from the reaction of 2-iodopyridine and thiophenol), R_f (hexane : EtOAc 8 : 2) = 0.54; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8.41 (dd, J_1 = 4.9 Hz, J_2 = 0.9 Hz, 1H), 7.62–7.54 (m, 2H), 7.45–7.37 (m, 4H), 6.99–6.94 (m, 1H), 6.86 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ161.3, 149.4, 136.6, 134.8, 130.8, 129.5, 129.0, 121.2, 119.7; MS (EI, 70 eV) m/z (% relative intensity, ion): 187 (28, [M$^+$]), 186(100) 78(13), 51(23).

3-Phenylthio-pyridine (3o)[16]. General procedure was followed (8 h), slightly yellow oil, 88 mg (0.47 mmol, 94% yield), R_f (hexane : EtOAc 6 : 4) = 0.57; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8.55 (s, 1H), 8.45 (d, J = 4.58 Hz, 1H), 7.59 (dt, J_1 = 7.9 Hz, J_2 = 1.6 Hz), 7.40–7.28 (m, 5H), 7.23–7.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 150.8, 147.7, 137.9, 133.8, 133.7, 131.7, 129.5, 127.8, 123.8; MS (EI, 70 eV) m/z (% relative intensity, ion): 187 (100, [M$^+$]), 115(15), 51(32).

4-(4-Methylphenylthio)-7-(trifluoromethyl)-quinoline (3p). General procedure was followed (16 h), yellow solid, 92 mg (0.29 mmol, 58% yield), mp.: 98–99 °C, R_f (hexane : EtOAc 8 : 2) = 0.53; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8.50 (d, J = 4.7 Hz, 1H), 8.27 (s, 1H), 8.50 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.63 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.67 (d, J = 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 150.5, 150.2, 146.5, 135.6, 131.8, 131.2, 131.0, 127.6(q), 127.3, 126.0, 124.7, 121.9(q), 121.6, 118.6, 21.3; MS (EI, 70 eV) m/z (% relative intensity, ion): 319 (100, [M$^+$]), 304(48), 207(18), 169(25), 91(32), 65(18). IR (ATR) 1326, 1284, 1162, 1148, 1120, 1066, 936, 806, 675 cm^{-1}, HRMS calcd for $C_{17}H_{13}F_3NS$ [M+H]$^+$ 320.0715, found 320.0716.

4-(4-Aminolphenylthio)-7-(trifluoromethyl)-quinoline (3q). General procedure was followed (24 h), yellow solid, 139 mg (0.43 mmol, 87% yield), mp.: 137–138 °C, R_f (hexane : EtOAc 1 : 1) = 0.53; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8.58 (d, J = 4.9 Hz, 1H), 8.35 (s, 1H), 8.27 (d, J = 8.7 Hz, 1H), 7.70 (dd, J_1 = 8.7 Hz, J_2 = 1.7 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.77–6.71 (m, 3H), 4.15(s, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 151.8, 150.4, 148.7, 146.3, 137.5, 131.6, 131.0, 127.4(q), 127.1, 126.0, 124.6, 121.7(q), 117.9, 116.2, 114.1; MS (EI, 70 eV) m/z (% relative intensity, ion): 320 (100, [M$^+$]), 207(22), 169(22), 124(68), 80(41), IR (ATR) 1560, 1332, 1304, 1222, 1196, 1146, 1116, 826, 664 cm^{-1}, HRMS calcd for $C_{16}H_{12}F_3N_2S$ [M+H]$^+$ 321.0668, found: 321.0664

4-(2-pyridylthio)-7-(trifluoromethyl)-quinoline (3r). General procedure was followed (24 h), yellow solid, 53 mg (0.17 mmol, 69% yield), mp.: 57–58 °C, R_f (hexane : EtOAc 1 : 1) = 0.40; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8.80 (d, J = 4.6 Hz, 1H), 8.44 (dd, J_1 = 4.9 Hz, J_1 = 0.9 Hz, 1H) 8.36 (s, 1H), 8.27 (d, J = 8.8 Hz, 1H), 7.64 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H), 7.57–7.48 (m, 2H), 7.19–7.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 155.6, 150.9, 150.6, 147.3, 143.1, 137.5, 132.0, 131.5, 129.4, 127.8(q), 126.2, 125.6, 125.4, 122.7(q), 122.2, 121.5; IR (ATR) 1574, 1557, 1453, 1416, 1326, 1286, 1193, 1111, 1066, 934, 831, 761, 680 cm^{-1}, HRMS calcd for $C_{15}H_{10}F_3N_2S$ [M+H]$^+$ 307.0511, found: 307.0511.

2-(4-Aminolphenylthio)-4-(trifluoromethyl)-pyrimidine (3s). General procedure was followed (24 h), yellow solid, 84 mg (0.31 mmol, 62% yield), mp.: 109–111 °C, R_f (hexane : EtOAc 1 : 1) = 0.65; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8.57 (d, J = 4.9 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 5.1 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 3.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 175.5, 159.6, 156.0, 155.4, 148.1, 136.9, 122.6, 117.9, 115.5, 115.4, 111.88, 111.84; MS (EI, 70 eV) m/z (% relative intensity, ion): 271 (100, [M$^+$]), 202(32), 124(90), 80(57), IR (ATR) 1568, 1496, 1325, 1284, 1165, 1119, 1067, 811, 676 cm^{-1}, HRMS calcd for $C_{11}H_9F_3N_3S$ [M+H]$^+$ 272.0464, found: 272.0466.

2-(2-Pyridylthio)-4-(trifluoromethyl)-pyrimidine (3t). General procedure was followed (24 h), yellow oil, 54 mg (0.20 mmol, 80% yield), R_f (hexane : EtOAc 1 : 1) = 0.54; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 8,67 (d, J = 4.9 Hz, 1H), 8,58 (d, J = 4.8 Hz, 1H), 7.75–7.71 (m, 2H), 7.30–7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 173.0, 159.8, 156.2, 155.7, 152.1, 150.3, 137.4, 129.9, 123.5, 122.1, 117.8, 112.80, 112.76; MS (EI, 70 eV) m/z (% relative intensity, ion): 257 (69, [M$^+$]), 199(52), 78(100), 51(59). IR (ATR) 1559, 1330, 1209, 1146, 1116, 833, 764, 732, 664 cm^{-1}, HRMS calcd for $C_{10}H_7F_3N_3S$ [M+H]$^+$ 258.0307, found: 258.0305

4-(4-Methoxyphenylthio)-benzophenone (3u)[18]. General procedure was followed, colourless crystals, X = Br (16 h) 106 mg (0.41 mmol, 82% yield), X = Cl (24 h) 110 mg (0.43 mmol, 85% yield); mp.: 39–40 °C, lit.: 40–41 °C, R_f (hexane : EtOAc 8 : 2) = 0.47; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.76 (dt, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 2H), 7.45 (dt, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 2H), 7.07 (dt, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 2H), 6.94 (dt, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 2H), 3.83 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 196.9, 160.5, 146.7, 136.7, 133.8, 128.7, 125.7, 121.3, 115.3, 55.3, 26.3; MS (EI, 70 eV) *m/z* (% relative intensity, ion): 258 (100, [M$^+$]), 243(85), 171(28), 139(25).

4-(4-Methoxyphenylthio)-benzonitrile (3v)[18]. General procedure was followed, colourless crystals, X = Br (16 h) 110 mg (0.46 mmol, 91% yield), X = Cl (48 h) 119 mg (0.49 mmol, 98% yield); mp.: 97–98 °C, lit.: 98–99 °C, R_f (hexane : EtOAc 8 : 2) = 0.60; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.48–7.40 (m, 4H), 7.05 (dt, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 2H), 6.96 (dt, J_1 = 9.0 Hz, J_2 = 2.6 Hz, 2H) 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 160.8, 147.2, 136.9, 132.1, 125.8, 120.1, 118.8, 115.4, 107.8, 55.3; MS (EI, 70 eV) *m/z* (% relative intensity, ion): 241 (100, [M$^+$]), 226(50), 196(13), 154(33), 63(20).

Acknowledgements

The authors thank for the generous research support and Graduate Scholarship for Sz. K. to Sanofi–Aventis, and Prof. K. Torkos, Dr Zs. Eke, Mr Sz. Nász for providing analytical support. Financial support and a Research Grant (Z. N.) from Magyary Zoltán Felsőoktatási Közalapítvány, EEA and Norway Grants are gratefully acknowledged. The work was also supported by OTKA-NKTH (CK 80763). The European Union and the European Social Fund have provided financial support to the project under the grant agreement no. TÁMOP 4.2.1./B-09/1/KMR-2010-0003.

Notes and references

1 T. Kondo and T. Mitsudo, *Chem. Rev.*, 2000, **100**, 3205.
2 (*a*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*b*) J.-P. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651; (*c*) H.-U. Blaser, A. Indolese, F. Naud, U. Nettekoven and A. Schnyder, *Adv. Synth. Catal.*, 2004, **346**, 1583; (*d*) L. Liu, J. E. Stelmach, S. R. Natarajan, M.-H. Chen, S. B. Singh, C. D. Schwartz, C. E. Fitzgerald, S. J. O'Keefe, D. M. Zaller, D. M. Schmatz and J. B. Doherty, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3979; (*e*) S. W. Kaldor, V. J. Kalish, J. F: Davies, B. V. Shetty, J. E. Fritz, K. Appelt, J. A. Burgess, K. M. Campanale, N. Y. Chirgadze, D. K. Clawson, B. A. Dressman, S. D. Hatch, D. A. Khalil, M. B. Kosa, P. P. Lubbehusen, M. A. Muesing, A. K. Patick, S. H. Reich, K. S. Su and J. H. Tatlock, *J. Med. Chem.*, 1997, **40**, 3979; (*f*) G. Liu, J. R. Huth, E. T. Olejniczak, F. Mendoza, S. W. Fesik and T. W. von Geldern, *J. Med. Chem.*, 2001, **44**, 1202; (*g*) S. F. Nielsen, E. Ø. Nielsen, G. M. Olsen, T. Liljefors and D. Peters, *J. Med. Chem.*, 2000, **43**, 2217; (*h*) G. De Martino, M. C. Edler, G. La Regina, A. Cosuccia, M. C. Barbera, D. Barrow, R. I. Nicholson, G. Chiosis, A. Brancale, E. Hamel, M. Artico and R. Silvestri, *J. Med. Chem.*, 2006, **49**, 947.
3 (*a*) T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato and M. Kosugi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1385; (*b*) M. Kosugi, T. Ogata, M. Terada, H. Sano and T. Migita, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3657.
4 (*a*) G. Y. Li, *Angew. Chem., Int. Ed.*, 2001, **40**, 1513; (*b*) M. A. Fernandez-Rodriguez, Q. Shen and J. F. Hartwig, *Chem.–Eur. J.*, 2006, **12**, 7782; (*c*) M. A. Fernandez-Rodriguez, Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 2180; (*d*) G. Y. Li, G. Zheng and A. F. Noonan, *J. Org. Chem.*, 2001, **66**, 8677; (*e*) T. Itoh and T. Mase, *Org. Lett.*, 2004, **6**, 4587; (*f*) C. C. Eichman and J. P. Stambuli, *J. Org. Chem.*, 2009, **74**, 4005; (*g*) M. A. Fernandez-Rodriguez and J. F. Hartwig, *J. Org. Chem.*, 2009, **74**, 1663; (*h*) Z. Jiang, J. She and X. Lin, *Adv. Synth. Catal.*, 2009, **351**, 2558.
5 V. P. Reddy, A. V. Kumar, K. Swapna and K. R. Rao, *Org. Lett.*, 2009, **11**, 1697.
6 (*a*) C. G. Bates, R. K. Gujadhur and D. Venkataraman, *Org. Lett.*, 2002, **4**, 2803; (*b*) F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3517; (*c*) Y.-J. Wu and H. He, *Synlett*, 2003, 1789; (*d*) C. G. Bates, P. Saejueng, M. Q. Doherty and D. Venkataraman, *Org. Lett.*, 2004, **6**, 5005; (*e*) W. Deng, Y. Zou, Y.-F. Wang, L. Liu and Q.-X. Guo, *Synlett*, 2004, 1254; (*f*) C. Palomo, M. Oiarbide, R. Lopez and E. Gomez-Bengoa, *Tetrahedron Lett.*, 2000, **41**, 1283; (*g*) C. Savarin, J. Srogl and L. S. Liebeskind, *Org. Lett.*, 2002, **4**, 4309; (*h*) P. S. Herradura, K. A. Pendola and R. K. Guy, *Org. Lett.*, 2000, **2**, 2019; (*i*) D. Zhu, L. Xu, F. Wu and B. Wan, *Tetrahedron Lett.*, 2006, **47**, 5781; (*j*) E. Sperotto, G. P. M. van Klink, J. G. de Vries and G. van Koten, *J. Org. Chem.*, 2008, **73**, 5625; (*k*) L. Rout, T. K. Sen and T. Punniyamurthy, *Angew. Chem., Int. Ed.*, 2007, **46**, 5583; (*l*) L. Rout, P. Saha, S. Jammi and T. Punniyamurthy, *Eur. J. Org. Chem.*, 2008, 640; (*m*) D. J. C. Prasad, Ajay B. Naidu and G. Sekar, *Tetrahedron Lett.*, 2009, **50**, 1411; (*n*) D. J. C. Prasad and G. Sekar, *Synthesis*, 2010, 79; (*o*) C.-K. Chen, Y.-W. Chen, C.-H. Lin, H.-P. Lin and C.-F. Lee, *Chem. Commun.*, 2010, **46**, 282; (*p*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*q*) F. Mauthner, *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 3593.
7 (*a*) X. Ku, H. Huang, H. Jiang and H. Liu, *J. Comb. Chem.*, 2009, **11**, 338; (*b*) W.-Y. Wu, J.-C. Wang and F.-Y. Tsai, *Green Chem.*, 2009, **11**, 326.
8 (*a*) E. Sperotto, G. G. M. van Klink, J. G. de Vries and G. van Koten, *J. Org. Chem.*, 2008, **73**, 5625; (*b*) V. P. Reddy, K. Swapna, A. V. Kumar and K. R. Rao, *Synlett*, 2009, 2783; (*c*) B. C. Ranu, A. Saha and R. Jana, *Adv. Synth. Catal.*, 2007, **349**, 2690.
9 (*a*) C. Gonzalez-Arellano, R. Luque and D. J. Macquarrie, *Chem. Commun.*, 2009, 1410; (*b*) S. Bhadra, B. Sreedhar and B. C. Ranu, *Adv. Synth. Catal.*, 2009, **351**, 2369; (*c*) A. V. Kumar;, V. P. Reddy and K. R. Rao, *Synlett*, 2010, 1260.
10 M. Martinek, M. Korf and J. Srogl, *Chem. Commun.*, 2010, **46**, 4387.
11 H. Wang, L. Jiang, T. Chen and Y. Li, *Eur. J. Org. Chem.*, 2010, **11**, 2324.
12 Fast disulfide formation from thiophenol was also observed in the absence of iodobenzene under argon (after 1 min in DMA at 100 °C). See ESI†.
13 C. G. Bates, R. K. Gujadhur and D. Venkataraman, *Org. Lett.*, 2002, **4**, 2803.
14 Y. C. Wong, T. T. Jayanth and C. H. Cheng, *Org. Lett.*, 2006, **8**, 5613.
15 B. Basu, B. Mandal, S. Das and S. Kundu, *Tetrahedron Lett.*, 2009, **50**, 5523.
16 V. P. Reddy, K. Swapna, A. V. Kumar and K. R. Rao, *J. Org. Chem.*, 2009, **74**, 3189.
17 J. Vicente, J. A. Abad and R. M. Lopez-Nicolas, *Tetrahedron*, 2008, **64**, 6281.
18 M. Arisawa, T. Suzuki, T. Ishikawa and M. Yamaguchi, *J. Am. Chem. Soc.*, 2008, **130**, 12214.

