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Copper-catalysed *N*-arylation of arylsulfonamides with aryl bromides and aryl iodides using KF/Al_2O_3

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Abstract. An efficient synthesis of *N*-arylsulfonamides with a variety of aryl bromides, aryl iodides and heteroaryl bromides using KF/Al_2O_3 as a suitable base, CuI as an inexpensive catalyst and *N,N′*-dimethylethylenediamine (*N,N′*-DMEDA) as an effective ligand is described.

Keywords. *N*-Arylsulfonamides; copper catalyst; *N*-arylation; KF/Al_2O_3; *N,N′*-dimethylethylenediamine.

1. Introduction

Formation of *C*(aryl)–*N* bond plays an important role in organic synthesis. Among the compounds possessing this bond, *N*-arylsulfonamides are important target molecules in pharmaceutical research. A number of these sulfonamides have been reported to show significant biological activity, e.g. non-nucleotide reverse transcriptase inhibitors,[1] class III antiarrhythmic agents[2] HIV-1 protease inhibitors[3] and non-peptidic vasopressin V1a receptor antagonists.[4] The vast majority of sulfonamides are prepared from the reaction of a sulfonyl chloride with ammonia or primary or secondary amines or via related transformations.[5] Because of difficulties in the preparation of sulfonyl chloride intermediate, sulfonamides are now mostly prepared through the direct formation of the aryl-nitrogen bond, using simple copper salt, copper metal or palladium complexes as a catalyst.[6] In 2003, Wu reported the CuI-catalysed *N*-arylation of sulfonamides with aryl bromides and aryl iodides under microwave irradiation.[7] Although no ligand was used in their study, the synthesis required a prolonged reaction time (2–4 h of microwave irradiation at 195°C) and the yields of the coupling products were modest (54–90%). To improve the efficiency of these methods, many ligands were used in the coupling reaction of sulfonamides with aryl halides.[8–10] However, many of reported procedures have drawbacks such as long reaction time, harsh reaction conditions, use of hygroscopic Cs_2CO_3 as base and carrying out reaction in a sealed tube. The application of KF/Al_2O_3 to organic synthesis has provided new methods for a wide array of organic reactions[11]. The strongly basic nature of KF/Al_2O_3 has allowed it to replace organic bases in a number of reactions.[12]

2. Experimental

All yields refer to isolated products. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. The ^{1}H NMR spectra were recorded on a Bruker DRX- 500 MHz Avance, Bruker 400 MHz Avance and Bruker DRX-300 MHz spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as internal standard.

2.1 *General procedure for the N-arylation of arylsulfonamides*

To a solution of aryl halide (1 mmol) and arylsulfonamide (1·5 mmol) in dioxane (5 mL) under argon atmosphere were added CuI (20 mol%) and *N,N′*-DMEDA (20 mol%) followed by KF/Al_2O_3[13] (5 equiv.). The reaction mixture was stirred at 100–

*For correspondence

110°C for the specified time (table 2). The reaction was monitored by TLC. At the end of reaction, mixture was cooled to room temperature. Ethyl acetate (50–60 mL) was added and filtrated. The filtrate was concentrated under vacuum and the residue subjected to column chromatography on silica gel using hexane: ethylacetate (70 : 30) as eluent to afford the pure coupled product. The spectroscopic data and melting points for known products agreed well with the reported data (table 2). Entry 1: A solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7·79–7·77 (*m*, 2H, Ar-H), 7·50 (*t*, 1H, *J* = 7·4 Hz, Ar-H), 7·41 (*t*, 2H, *J*=7·4 Hz, Ar-H), 7·22 (*t*, 2H, *J* = 7·8 Hz, Ar-H), 7·09–7·06 (*m*, 4H, Ar-H and NH)· Entry 3: A solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7·77–7·75 (*m*, 2H, Ar-H), 7·50–7·47 (*m*, 1H, Ar-H), 7·41–7·38 (*m*, 2H, Ar-H), 7·10 (*br s*, 1H, NH), 7·00–6·94 (*m*, 4H, Ar-H), 2·23 (*s*, 3H, CH_3). Entry 4: A solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·64 (*d*, 2H, *J* = 8·3 Hz, Ar-H), 7·22 (*d*, 2H, *J* = 8·0 Hz, Ar-H), 7·03 (*d*, 2H, *J* = 8·3 Hz, Ar-H), 6·97–6·93 (*m*, 2H, Ar-H), 6·62 (*br s*, 1H, NH), 2·38 (*s*, 3H, CH_3), 2·27 (*s*, 3H, CH_3). Entry 8: A solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·58 (*d*, 2H, *J* = 8·2 Hz, Ar-H), 7·22 (*d*, 2H, *J* = 8·2 Hz, Ar-H), 6·99–6·94 (*m*, 2H, Ar-H), 6·79–6·74 (*m*, 2H, Ar-H), 6·32 (*br s*, 1H, NH), 3·76 (*s*, 3H, OCH_3), 2·39 (*s*, 3H, CH_3). Entry 10: A solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·82–7·79 (*m*, 2H, Ar-H), 7·60–7·55 (*m*, 1H, Ar-H), 7·38-7·34 (*m*, 2H, Ar-H), 7·32–7·27 (*m*, 2H, Ar-H), 6·98 (*br s*, 1H, NH). Entry 12: A solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·83–7·73 (*m*, 5H, Ar-H), 7·51–7·34 (*m*, 7H, Ar-H), 6·81 (*br s*, 1H, NH). Entry 16: A solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·70 (*d*, 2H, *J*= 8·2 Hz, Ar-H), 7·22 (*d*, 2H, *J* = 8·2 Hz, Ar-H), 7·10 (*t*, 1H, *J* = 7·8 Hz, Ar-H), 6·98 (*br s*, 1H, NH), 6·89 (*t*, 3H, *J* = 6·8 Hz, Ar-H), 2·37 (*s*, 3H, CH_3), 2·26 (*s*, 3H, CH_3). Entry 19: A solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11·18 (*s*, 1H, NH), 8·11 (*d*, 2H, *J* = 9·1 Hz, Ar-H), 7·74 (*d*, 2H, *J* = 8·2 Hz, Ar-H), 7·37 (*d*, 2H, *J* = 8·2 Hz, Ar-H), 7·29 (*d*, 2H, *J* = 9·1 Hz, Ar-H), 2·32 (*s*, 3H, CH_3). Entry 20: A solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·85 (*d*, 4H, *J* = 8·6 Hz, Ar-H), 7·57 (*t*, 1H, *J* = 6·0 Hz, Ar-H), 7·47 (*t*, 2H, *J* = 7·1 Hz, Ar-H), 7·16 (*d*, 2H, *J* = 8·6 Hz, Ar-H), 7·12 (*br s*, 1H, NH), 2·53 (*s*, 3H, $COCH_3$). Entry 21: A solid, ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10·77 (*br s*, 1H, NH), 7·81 (*d*, 2H, *J* = 8·4 Hz, Ar-H), 7·70 (*d*, 2H, *J* = 7·9 Hz, Ar-H), 7·35 (*d*, 2H, *J* = 7·9 Hz, Ar-H), 7·19 (*d*, 2H, *J* = 8·4 Hz, Ar-H), 2·44 (*s*, 3H, $COCH_3$), 2·31 (*s*, 3H, CH_3). Entry 23: A solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11·87 (*br s*, 1H, NH), 8·01 (*br s*, 1H, Het-H), 7·76 (*d*, 2H, *J* = 7·6 Hz, Ar-H), 7·70 (*t*, 1H, *J* = 7·6 Hz, Het-H), 7·33 (*d*, 2H, *J* = 7·6 Hz, Ar-H), 7·14 (*br d*, 1H, *J* = 7·6 Hz, Het-H), 6·86 (*br s*, 1H, Het-H), 2·33 (*s*, 3H, CH_3). Entry 24: A solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10·58 (*br s*, 1H, NH), 8·43 (*br s*, 1H, Het-H), 7·77 (*d*, 2H, *J* = 7·2 Hz, Ar-H), 7·64–7·51 (*m*, 6H, Ar-H and Het-H), 7·36 (*br s*, 1H, Het-H). Entry 26: A solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7·70 (*d*, 2H, *J* = 8·0 Hz, Ar-H) 7·38 (*br s*, 1H, NH), 7·24 (*d*, 2H, *J* = 8·0 Hz, Ar-H), 7·17 (*dd*, 1H, *J* = 5·2 and 3·2 Hz, Het-H), 6·89–6·86 (*m*, 2H, Het-H), 2·39 (*s*, 3H, CH_3).

3. Results and discussion

In our procedure we have used a stable and suitable base, KF/Al_2O_3, for *N*-arylation of arylsulfonamides with aryl bromides, aryl iodides and heteroaryl bromides (scheme 1).

In order to find the optimum reaction conditions we have treated 4-iodotoluene with benzenesulfonamide with KF/Al_2O_3, CuI (20 mol%) in dioxane in the presence of different ligands such as 1,10-phenanthroline, *L*-proline, *N,N*′-dibenzylethylenediamine, *N,N*′-dimethylethylenediamine, glycine,

Table 1. The coupling of 4-iodotoluene with benzenesulfonamide in the presence of different ligands.

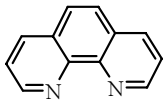
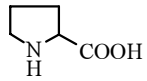
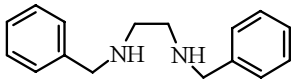
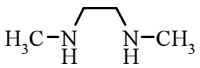
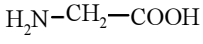
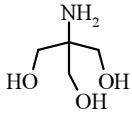
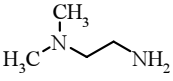
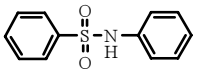
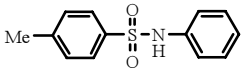
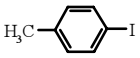
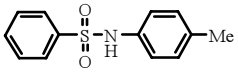
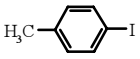
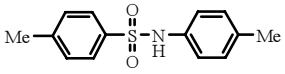
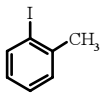
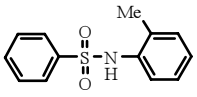
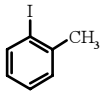
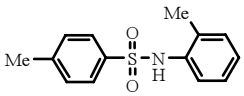
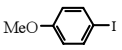
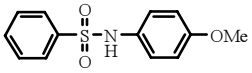
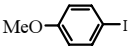
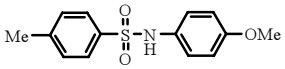
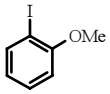
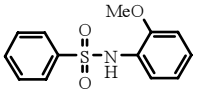
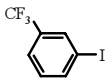
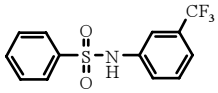
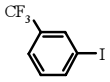
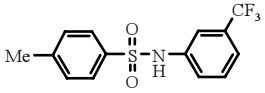
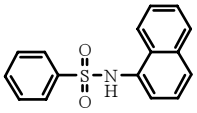
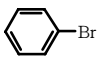
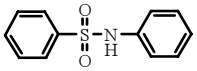
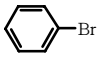
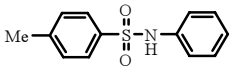
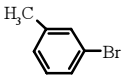
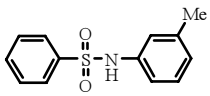
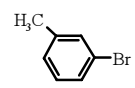
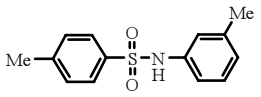
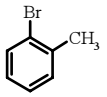
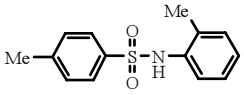
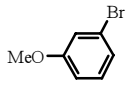
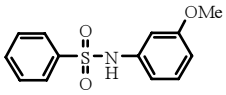
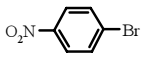
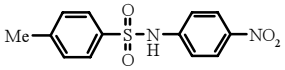
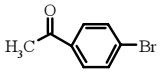
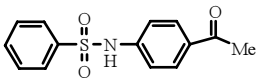
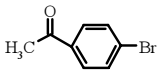
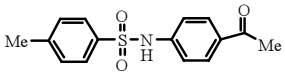
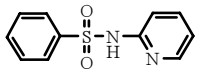
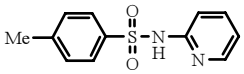
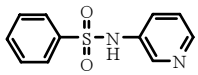
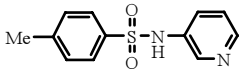
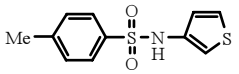
Entry	Ligand	Yield (%)
1		45
2		55
3		20
4		90
5		40
6		15
7		30

Table 2. The copper-catalysed *N*-arylation of arylsulfonamides in the presence of KF/Al_2O_3.

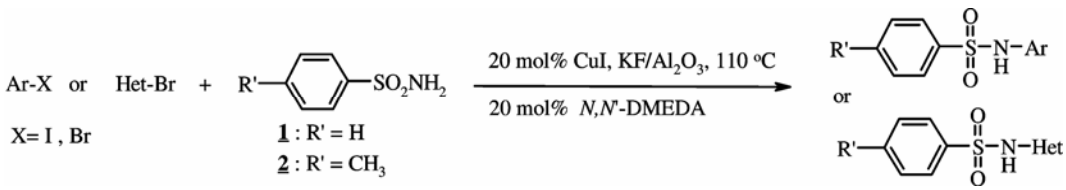
Entry	Aryl halide or Het-Br	Sulfonamide	Product[a]	Time (h)	M.p. (°C) Observed (reported)[15]	Yield (%)[b]
1		**1**		9	109–112 (111–112)[15a]	91
2		**2**		9	97–99 (102–103)[15b]	93
3		**1**		9	118–120 (117–119)[15c]	90
4		**2**		8	117–118 (115)[15b]	92
5		**1**		13	120–122 (122–123)[15d]	15
6		**2**		13	105–107 (107–109)[15e]	15
7		**1**		11	93–94·5 (88–89)[15f]	75
8		**2**		10	112–114 (114)[15g]	86
9		**1**		13	87–89 (88–89)[15h]	42
10		**1**		5	72·5–74 (88–89)[15i]	88
11		**2**		5	94·5–96·5 (94–95·5)[15j]	88
12		**1**		12	168–170 (170·5–171·5)[15k]	40
13		**1**		11	109–112 (111–112)[15a]	80
14		**2**		11	97–99 (102–103)[15b]	84
15		**1**		12	94·5–95·5 (95)[15l]	86

(*Contd…*)

Table 2. (*Contd…*)

Entry	Aryl halide or Het-Br	Sulfonamide	Product[a]	Time (h)	M.p. (°C) Observed (reported)[15]	Yield (%)[b]
16		**2**		12	114–115·5 (114)[15m]	86
17		**2**		13	105–107 (107–109)[15e]	15
18		**1**		13	79·5–81·5 (82·5–83·5)[15d]	66
19		**2**		6	193–196 (189–191)[15n]	96
20		**1**		11	258–260 (262)[15o]	90
21		**2**		10	204–206 (204·5–205)[15p]	94
22		**1**		4	171–173 (171–172)[15q]	98
23		**2**		4	214–216 (215–216)[15r]	90
24		**1**		12	191–193 (188·1–189·1)[15s]	85
25		**2**		12	192–194 (190·5–191·5)[15t]	85
26		**2**		13	106–108 (105–106)[15v]	75

[a]Reactions performed using 20 mol% of *N,N′*-DMEDA as ligand, 1.0 equiv. of aryl halide or heteroaryl bromide, 1·5 equiv. of arylsulfonamides and 5 equiv. of KF/Al_2O_3 as base in dioxane as solvent at 100–110°°C. [b]Isolated yields; products were characterized by ^1H NMR and melting points



Scheme 1. *N*-Arylation of arylsulfonamides catalysed by CuI and KF/Al_2O_3.

tris(hydroxymethyl)aminomethane and *N,N*-dimethylethylenediamine and the results are presented in table 1. The best yield of the cross-coupling product was obtained with *N,N′*-DMEDA (table 1, entry 4).

KF/Al_2O_3 as a base in the presence of CuI was chosen as we have recently used this system for C–N and C–O bond formation in arylation of amide, alcohols, phenols and diazoles.[14] To test the generality of this procedure, we have examined the coupling of different aryl iodides, aryl bromides and heteroaryl bromides with benzene and *p*-toluenesulfonamides and results are shown in table 2.

When iodobenzene was treated with sulfonamides under optimal reaction conditions, a high yield of the coupling products was obtained (table 2, entries 1 and 2). Similarly, *para*- methyl and *para*-methoxy iodobenzene with sulfonamides gave the corresponding *N*-arylsulfonamides in high yield (table 2, entries 3, 4 and 7, 8). However, when *ortho*-methyl, *ortho*-methoxy iodobenzenes or 1-iodonaphtalene were used, the yield of the products were low (table 2, entries 5, 6 and 9, 12). Longer reaction time and caring out the reaction in a solvent at a high temperature did not improve the yield. On the other hand, when electron withdrawing groups are present on the aryl iodide the reaction was faster and the yield of the coupled product high (table 2, entries 10 and 11). We have tried to extend this protocol to aryl bromides and aryl chlorides. Aryl bromides under the same reaction conditions when treated with sulfonamides, gave the same results (table 2, entries 13–21), but aryl chlorides did not give satisfactory results and in most cases the reaction material was recovered unchanged. Interestingly, the reaction of heteroaryl bromides such as 2-bromopyridine, 3-bromopyridine, or 3-bromothiophen with benzene or *p*-toluene sulfonamides gave the corresponding *N*-(heteroaryl)benzenesulfonamide in good yields (table 2, entries 22–26).

4. Conclusion

In summary, we have developed a simple and efficient method for the copper-catalysed coupling of a variety of aryl iodides, aryl bromides and heteroaryl bromides with benzene and *p*-toluene sulfonamides using KF/Al_2O_3, CuI and *N,N′*-DMEDA. Potassium fluoride supported on alumina (KF/Al_2O_3) provides a viable alternative to bases such as Cs_2CO_3.

Acknowledgement

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