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TBAHS CATALYZED COUPLING REACTIONS OF ARYL IODIDES AND ARYL BROMIDES WITH THIOLS UNDER SOLVENT FREE CONDITIONS

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Abstract
A recyclable and efficient Tetrabutylammonium hydrogensulfate (TBAHS) catalysed coupling reaction of aryl halides (iodide and bromide) with aryl and alkyl thiols under solvent-free conditions were developed.

Keywords: Thiols, aryl halides, catalysts, ionic liquid.

Introduction

The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, that are widely used in organic synthesis have posed a serious threat to environment.[I-V] The advantage of the elimination of highly toxic co-solvent, the ease of work-up (product can be isolated from the reaction mixture either by decantation or extraction with a variety of solvents), and the possibility of the recycling the catalyst have already been demonstrated.[IV] Thus, design of solvent-free reactions[I] and use of alternative green solvents like water,[II] supercritical fluids[III] and ionic liquids[IV] have received much attention in recent times in the area of green synthesis. Although ionic liquids have been successfully employed as solvents with catalytic activities for a variety of important reactions[IV] their use as real catalyst under solvent-free conditions has not much explored.[V]

Methods for the preparation of various alkyl aryl sulphides are indispensable in organic[VI,VII] and medicinal chemistry.[VIII] Consequently, numerous synthetic methods for alkyl aryl sulfide formation have been developed. Generally synthesis of aryl sulphides are accomplished by; (i) coupling of aryl halides with thiols in HMPA at 200^{o}C using copper salts[IX]; (ii) coupling of aryl iodides with thiols in toluene at 110 ^{o}C using 10 mol% CuI and, 10 mol% neocuproine[10]; (iii) Cu-catalysed C-S coupling reactions of aryl iodidesand thiols using 5 mol% CuI and 2 equivalents of $HOCH_2CH_2OH$ as ligand[XI]; (iv) CuI catalysed arylation of I-thiosugars[XII] and (v) arylation of thiols using 5 mol% CuI and 20 mol% amino acid as ligand.[XIII]

Transition metal-catalysed and mediated methods for the construction of aryl-sulfur bonds[XIV] have usually required either forcing reaction conditions[XV] or substrates with ortho carbonyl groups that are both electron withdrawing and capable of chelating copper.[XVI]
In the present account we investigated the cross coupling reaction of aryl iodides and aryl bromides with thiols under solvent free condition using TBAHS as ionic liquid.

Experimental Section
Bromobenzene and octylthiol was used as a prototypical combonation for prelimnary optimisation of the reaction conditions. Number of bases, solvents and reaction conditions were screened for the standardization of the test reaction of bromobenzene and octanethiol using tetrabutylammonium hydrogensulfate as a catalyst (Table 1).

In the absence of tetrabutylammonium hydrogensulfate no aryl sulfide was detected (entry 1). When Cs_2CO_3 was used as a base in the coupling reaction of bromobenzene with octanetiol using 30 mol % of TBAHS as a catalyst GC analysis shows the formation of phenyl octyl sulfide in less than 48% (entry 5). Best coupling results were obtained using 2 equiv of KOBu^t and 30-mol% of TBAHS catalyst under solvent free condition (Table 1).

A wide range of structurally varied aromatic thiols underwent clean arylations with a variety of aryl iodides and aryl bromides to provide C-S bond formation in very high yields. The results are summarized in Table 2. The experimental procedure is very simple. A mixture of aryl halide, base and thiol was added to tetrabutylammonium hydrogensulphate and was stirred at 100-110 ^oC for required time (see Table 2). The product was isolated either by direct distillation under reduced pressure or extraction with a relatively diethyl ether. The tetrabutylammonium hydrogensulphate remained in the reaction flask washed with hexane, dried under vacuum and recycled for subsequent uses without any loss of efficiency. 30 mol% of tetrabutylammonium hydrogensulphate (with respect to thiol) was found to be optimum for an efficient, clean and fast reaction.

Reactions Condition
Entry 1 in Table 2), A mixture of benzenethiol (300mg, 1.1 equiv.), KOBu^t (555mg, 2.0 equiv.) and iodobenzene (1.01g, 2.0 equiv.) was added to tetrabutylammonium hydrogensulfate (30 mol%) and whole mixture was stirred at 100-110 ^oC for 58 minutes (Reaction was monitored by TLC). The product was isolated by direct distillation under reduced pressure from the reaction mixture as liquid in 98%, whose spectral data (IR, ^{1}H NMR, ^{13}C NMR and Mass) are in good agreement with that reported.[X, XVI]

All other reactions listed in Table 2 and Table 3 were carried out by following the above procedure. The distillation was not very convenient, the product could be isolated by extraction with diethylether followed by washing with 10% NaOH solution, brine and purification by column chromatography. All the product were fully characterized by their ^{1}H NMR, ^{13}C NMR and Mass spectral data, all of them have been reported earlier[VII-XIX] except 1-(2-Methoxy-phenylsulfanyl)-naphthalene. 1-(2-Methoxy-phenylsulfanyl)-naphthalene (Entry 9 in Table 2): Pale yellow semisolid. ^{1}HNMR ($CDCl_3$, 300MHz): δ =7.73 (d, J = 7.8 Hz, 2H), 7.68-7.63 (m, 2H), 7.27-7.22 (m, 3H), 6.75 (d, J = 6Hz, 2H), 6.61 (t, J = 7.5Hz, 2H), 3.28 (s, 3H). ^{13}CNMR

($CDCl_3$, 300MHz): δ = 157.8, 139.2, 129.4, 128.4, 127.5, 126.8, 126.4, 125.3, 122.2, 110.8, 85.8, 56.0. MS (EI): m/z: 266.3, 159.3, and 107.1.

Results and Discussion

A variety of functionalities such as Cl, NO_2, OMe, $COCH_3$, CHO, also survived in the present reaction conditions. No aryl sulfide has been observed with tetrabutylammonium hydrogensulfate at room temperature or under reflux in dichloromethane and dichloroethane.

A competitive experiment in which 1 equiv. of octanethiol and 1 equiv. of KO*t*-Bu were treated with 1 equiv. of 1-bromo-4-iodobenzene (Scheme 1) was undertaken and it was found that in this case, not only 1-bromo-4-octylsulfanyl-benzene (57%) but also 1, 4-bis-octylsulfanyl-benzene (19%) were isolated. This result clearly indicated that thiol couple readily with iodobenzene.

Alkylthiols were also found to be effective nucleophiles under these reaction conditions (Table 3). Cyclohexylmercaptan and benzylmercaptan were S-arylated in excellent yields (enteries 1 and 3). Our reaction protocol does not require the use of expensive transition metal catalyst and ligand, thus allowing the formation of aryl sulfide.

Compared with traditional solvents and reported catalysts, easy recycling is an attractive property of tetrabutylammonium hydrogensulphate as IL. Consequently, we investigated the catalytic activity of recycled TBAHS in the reaction of bromobenzene and thiophenol. As shown in Fig. 1, TBAHS could be reused at least three times without significant loss of activity.

Figures:

Fig. 1 Recyling of TBAHS in the reaction of bromobenzene and thiophenol (75 min, 100 ^oC).

Schemes:

Scheme 1

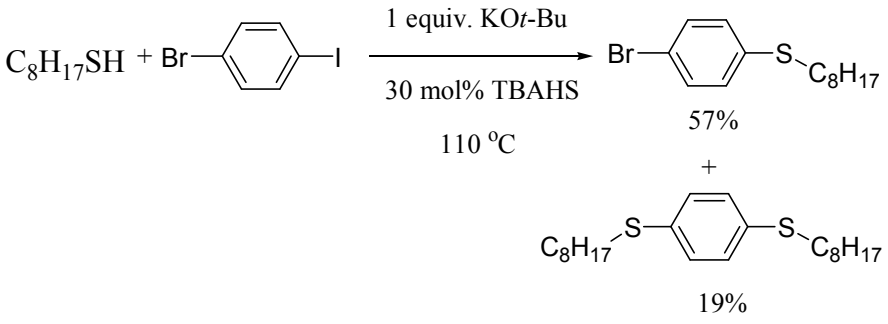
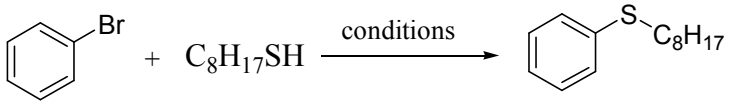


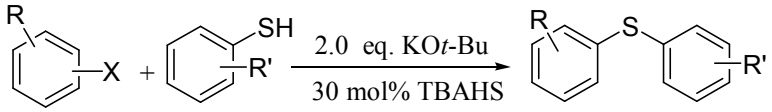
Table 1 Evaluation of different catalyst systems for the formation of phenyl octyl sulfide[a]

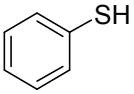
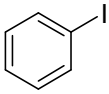
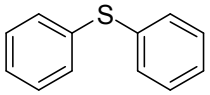
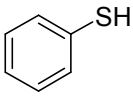
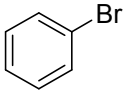
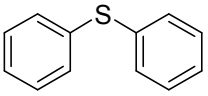
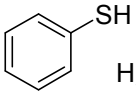
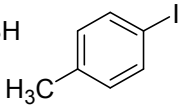
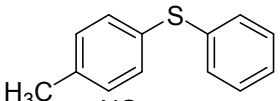
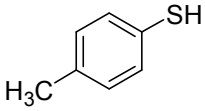
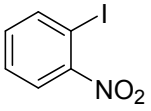
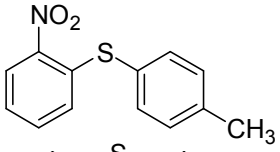
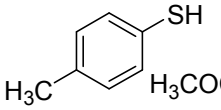
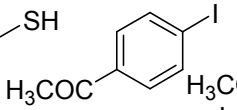
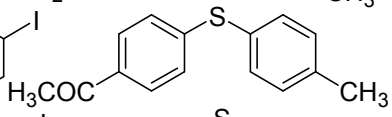
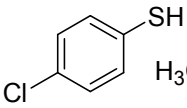
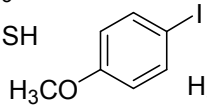
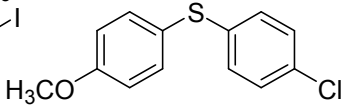
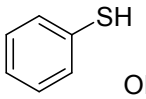
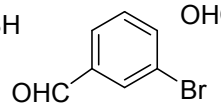
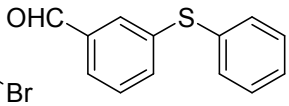
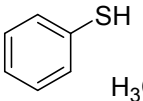
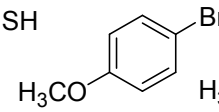
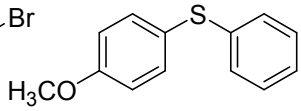
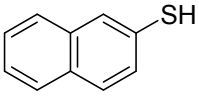
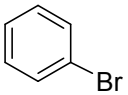
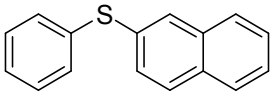


Entry	conditions[a]	% Yield
1	KO*t*-Bu, DMSO, 120 °C	nd
2	TBAHS,[b] KO*t*-Bu, n-BuOH, 120 °C	nd
3	TBAHS,[c] KO*t*-Bu, toluene, 120 °C	nd
4	TBAHS,[d] K_2CO_3, 120 °C	29
5	TBAHS,[e] Cs_2CO_3, 120 °C	48
6	TBAHS,[f] KO*t*-Bu, 110 °C	90

[a]Reactions were conducted with 1.1 equiv. of n-octanethiol, and 2.0 equiv. of base for 5 h with 2.0 equiv. of bromobenzene. [b] 5 mol% of TBAHS, purchased from Aldrich. [c] 5 mol% of TBAHS, purchased from Aldrich. [d, e, f] 30 mol% of TBAHS under solvent-free condition. nd means not determined.

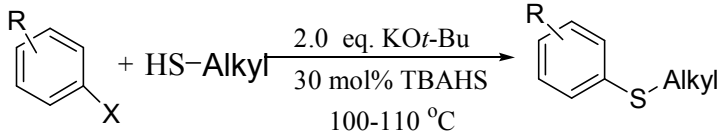
Table 2 TBAHS catalyzed Carbon-sulfur bond formation of aryl thiols[a]

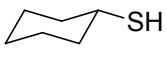
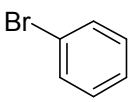
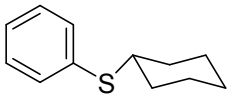
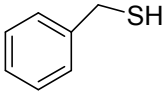
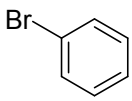
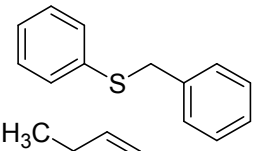
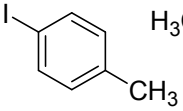
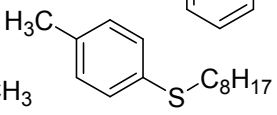
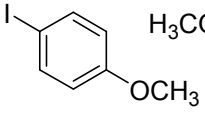
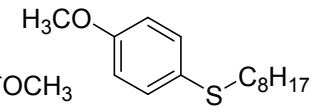
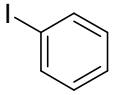
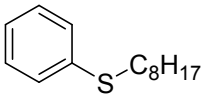
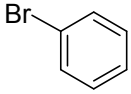
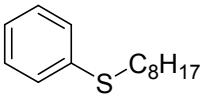


Entry	Thiols	Aryl halide	Product	Time (min)	Yield (%)[b]
1				58	98
2				75	90
3				60	95
4				95	88
5				108	72
6				65	94
7				125	88
8				120	80
9				95	85

[a]General conditions: 30 mol% TBAHS, 1.1 equiv. of thiol, 2.0 equiv. of base , 2.0 equiv. of aryl halide, reaction temperature = 100-110 °C. [b] Isolated yields.

Table 3 TBAHS catalyzed Carbon-sulfur bond formation of alkyl thiols[a]



Entry	Thiols	Aryl halide	Product	Time (min)	Yield (%)[b]
1				85	86
2				79	95
3	$C_8H_{17}SH$			60	96
4	$C_8H_{17}SH$			60	94
5	$C_8H_{17}SH$			80	92
6	$C_8H_{17}SH$			89	90

[a]General conditions: 30 mol% TBAHS, 1.1 equiv. of thiol, 2.0 equiv. of KO*t*-Bu, 2.0 equiv. of aryl halide, reaction temperature=100-110 °C. [b] Isolated yields.

Conclusions

In conclusion, the present solvent-free procedure for arylation of aryl and alkyl-thiols demonstrates the potential of tetrabutylammonium hydrogensulfate, a cheap readily available ionic liquid as an efficient catalyst and thus broadens the scope for catalytic uses of ionic salts for organic transformations in general. Moreover, this methodology offers significant improvements over many existing procedures with regard to yield of products, mildness of

reaction conditions, simplicity in operation, cost-efficiency, and above all, green aspects avoiding toxic catalysts and solvents.

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