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Chloride based ionic liquids as promoting agents for Meerwein reaction in solventless conditions

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Abstract—Chloride based ionic liquids were used as chloride source in Meerwein reaction either in [bmim]X (bmim = 1-butyl-3-methylimidazolium, X = BF_4, PF_6) as solvents or in solventless conditions. Satisfactory yields (49–71%) with diversely substituted diazonium salts were achieved by using 1,3-dibutylimidazolium chloride in the presence of a bimetallic Zn/Cu catalyst.

The Meerwein reaction, the copper catalyzed formal addition of an aryl halide to an activated olefin,[1] is a useful tool for the synthesis of building blocks for the preparation of a series of heterocyclic compounds such as substituted indoles,[2] substituted quinolinones,[3] benzothiophenes[4] and benzylthiazolidine-2,4-diones,[5,6] the latter class of compounds finding some important pharmaceutical application.

In the classic procedure of the Meerwein reaction, the aniline is diazotized in aqueous media in the presence of the appropriate halide. The resulting aryldiazonium halide solution is added to a water–acetone solution of the olefinic compounds in the presence of a cupric salt as catalyst.[1] This protocol requires the control of a large number of experimental variables that strongly influence the efficiency and reproducibility of the process: pH of the reaction media, total halide concentration, reaction temperature, catalyst load, composition of the water–acetone mixture and the extent of the excess of the olefin employed. Generally, every substrate preliminarly needs reaction parameter optimization in order to get fair yields. Although the Meerwein reaction has been extensively studied[7–12], its mechanism is still not clear. However, many evidences point out the existence of a radical chain mechanism triggered by cuprous species originated by preliminary reduction of the cupric salt in the reaction medium.[9,12]

Looking for a more general protocol that would overcome the abovementioned experimental difficulties, Doyle et al.[13] proposed the copper mediated deamination of anilines by alkyl nitrite in the presence of unsaturated compounds. In this procedure, *tert*-butyl nitrite is added to an anhydrous acetonitrile solution of the appropriate aniline, anhydrous cupric halide and olefinic compound. In this way, aniline was diazotized in situ and reacted with the olefin by intermediacy of copper. Arylated products are generally obtained in satisfactory yields but this protocol requires more than a stoichiometric amount of copper salt (1.2 equiv with respect to the aniline) that constitutes the principal drawback of the proposed procedure. Recently, Obushak et al.[14] suggested the reaction of diazonium tetrahalocuprates in mixed water–acetone solvent in the presence of olefin as a valid alternative to the classical Meerwein protocol. The yields of arylated products were good but the very high load of copper (50% mol with respect to the diazonium ion) renders this reaction not assimilable to a metal catalyzed process.

Ionic liquids (ILs) have attracted the interest of many researchers. Their peculiar physical–chemical properties render ILs particularly interesting as solvents for a wide range of processes.[15] In particular, metal catalyzed C–C bond forming reactions can be successfully performed in ILs with improved catalyst efficiency.[16] To the best of our knowledge, only three reports deal with the reactivity of diazonium salts in ILs.[17–19]

Moreover, the efficiency of copper mediated radical process could be improved in ILs.[20] This led us to

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Keywords: Meerwein reaction; Ionic liquids; Diazonium tetrachlorozincate.

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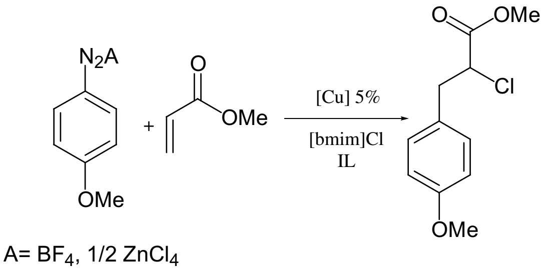
investigate the feasibility of Meerwein reaction in such reaction media.

p-Methoxyphenyldiazonium complex salt and methyl acrylate were chosen as reagents in a model system (Scheme 1). The reactions, which were completed in less than 30 min, were conducted with a copper load of 5% in mol with respect to the diazonium salt, using [bmim]Cl as the chloride source. The results obtained using [bmim]BF_4 or [bmim]PF_6 as solvents or in 'solventless' conditions are listed in Table 1.

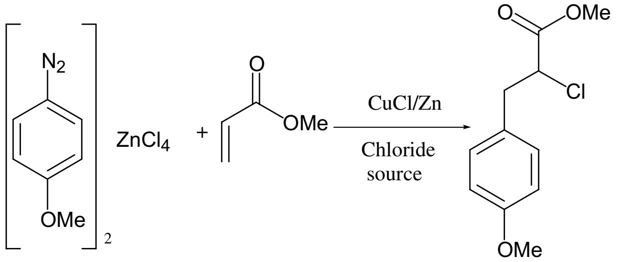
Differently from cupric chloride which gave no reaction (entry 1) the corresponding cuprous salt was active (entry 2), suggesting that copper(II) does not undergo reduction to copper(I)[9,12] in IL. Passing from [bmim]BF_4 to [bmim]PF_6 resulted in a higher yield (entries 2 and 3). However, the reaction could be successfully carried out by using solely [bmim]Cl at the same time as the chloride source and phase transfer agent. Moreover, in such experimental conditions the diazonium tetrachlorozincate salt[21] revealed to be a viable alternative to the more expensive tetrafluoroborate analogue (entries 4 and 5) and the resulting yield was comparable to that obtained in [bmim]PF_6 (entries 3 and 5). The efficiency of the process was affected by the composition of the system: reducing or increasing the amount of the available chloride resulted in a decrease of product yield (compare entry 5 with entries 6 and 7). In the absence of [bmim]Cl, no reaction took place between the diazonium tetrachlorozincate and the olefin (entry 8), presumably due to the insolubility of cuprous chloride and diazonium salt in methyl acrylate.

Other azolium salts were tested as phase transfer agent-chloride source, in 'solventless' conditions (Scheme 2). The reactions carried out in these conditions needed particular care in order to minimize moisture contamination, which was found to affect the reproducibility of the results. We observed a correlation between partial conversion (β-naphthol test) and the ageing of reaction solution comprised methyl acrylate, chloride salt and CuCl. Full reproducibility was achieved by addition of a catalytic amount of Zn dust. In this way, complete and reproducible reactions were achieved (Table 2) without any special care in storing reagent and performing reactions. The yields were found dependant on the IL cation — imidazolium based ILs being superior compared with butylpyridinium (entry 1) and tetrabutylammonium (entry 2). In particular, the reaction carried out in the presence of 1,3-dibutylimidazolium chloride ([dbim]Cl) gave a 72% yield (entry 5), which compares well with that obtained in [bmim]PF_6.

The detrimental role of moisture was confirmed by carrying out the reaction in [dbim]Cl with deliberately added water. In this case, the time to reach reaction completion doubled and the obtained yield was significantly lower (entry 6). The water present in the reaction media presumably interferes with the redox couple Cu(I)/Cu(II), which is postulated to be involved in the catalytic cycle of Meerwein reaction.[7–14] In fact, the presence of water can cause a shift of redox equilibrium favoring the Cu(II) form[22] with consequent inhibition of catalysis. A possible catalytic activity of solely zinc dust was ruled out by a blank test, which gave no conversion after 3 h. Reasonably, zinc acts as reductant towards



Scheme 1.



Scheme 2.

Table 1.

Entry	Solvent	[bmim]Cl (mmol)	A^-	Catalyst	Methyl acrylate (mmol)	Yield (%)[a]
1	[bmim]BF_4	10	BF_4	$CuCl_2 \cdot 2H_2O$	11	—
2	[bmim]BF_4	10	BF_4	CuCl	11	59[b]
3	[bmim]PF_6	10	BF_4	CuCl	11	68[b]
4	—	10	BF_4	CuCl	55	54
5	—	10	$ZnCl_4$	CuCl	55	64
6	—	5	$ZnCl_4$	CuCl	55	54
7	—	15	$ZnCl_4$	CuCl	55	58
8	—	—	$ZnCl_4$	CuCl	55	—

Reaction conditions. Ionic liquid: 5.0 mL (when used); *p*-methoxyphenyldiazonium salt (5 mmol of BF_4 salt or 2.5 mmol of $ZnCl_4$ salt); CuCl: 0.125 mmol; reaction time: 30 min; room temperature; [bmim] = 1-butyl-3-methylimidazolium.

[a] GLC yield.

[b] Isolated yield.

Table 2.

Entry	Chloride source	Time (h)	Yield (%)[a]
1	[bupy]Cl	1	45
2	[tba]Cl	0.5	42
3	[bmim]Cl	0.5	59
4	[bdmim]Cl	1.5	52
5	[dbim]Cl	0.5	72
6	[dbim]Cl[b]	1	41

Reaction conditions: *p*-methoxyphenyldiazonium tetrachlorozincate double salt: 2.50 mmol; methyl acrylate: 5.0 mL; azolium salt: 10 mmol; CuCl: 0.125 mmol; Zn dust: 0.250 mmol; room temperature. [bupy] = butylpyridinium, [tba] = tetrabutylammonium, [bdmim] = 1,2-dimethyl-3-butylimidazolium, [dbim] = 1,3-dibutylimidazolium.

[a] GLC yield.

[b] Without Zn and with 5 μL of water added to the reaction mixture.

$$Zn + Cu^{2+} \longrightarrow Zn^{2+} + Cu^0$$

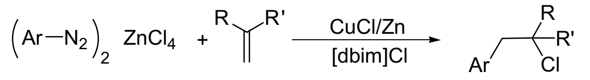
$$Cu^{2+} + Cu^0 \longrightarrow 2\,Cu^+$$

Scheme 3.

Cu(II) forming Cu(0) which reacts with residual Cu(II) generating the active Cu(I) species (Scheme 3).

The protocol based on bimetallic Zn/Cu catalyst and [dbim]Cl was extended to other substrates (Scheme 4). The results are listed in Table 3.

The reactions were fast (completion was reached in less than 30 min) and reproducible. The yields ranged from 49% to 71%. Activated olefins such as ethyl methacrylate (entry 1), acrylonitrile (entry 2), and styrene (entry 3) gave yields of about 60%. The substituent on the aromatic core of aryldiazonium ions influenced the reaction course,[13] electron-donating groups generally decreasing the yields. Interestingly, in our system comparable yields were obtained with electron-withdrawing as well as with electron-donating substituted aryldiazonium salts (entries 4, 5 and 6 of Table 3 and entry 5 of Table 2). A satisfactory 71% yield was achieved with the methyl substituted diazonium ion (entry 7 of Table 3). The relative position of the substituent with respect to the diazo group did not exert a remarkable effect on the reaction course (entry 8 of Table 3 and entry 5 of Table 2). Among the ortho substituted diazonium tetrachlorozincates, those bearing 2,5-$(MeO)_2C_6H_4$ or 1-naphthyl gave about 50% yield (entries 9 and 10), whereas the 2,4-dichlorophenyldiazonium salt afforded 68% yield (entry 11).



Scheme 4.

Table 3.[23]

Entry	Ar	R	R′	Yield (%)[a]
1	*p*-$MeOC_6H_4$	COOEt	Me	58
2	*p*-$MeOC_6H_4$	CN	H	61
3	*p*-$MeOC_6H_4$	Ph	H	63
4	*p*-$NO_2C_6H_4$	COOMe	H	65
5	*p*-$COOEtC_6H_4$	COOMe	H	59
6[24]	*p*-$CH_3CONHC_6H_4$	COOMe	H	54
7	*p*-$CH_3C_6H_4$	COOMe	H	71
8	*m*-$MeOC_6H_4$	COOMe	H	63
9	2,5-$(MeO)_2C_6H_3$	COOMe	H	50
10	1-Naphthyl	COOMe	H	49
11	2,4-$Cl_2C_6H_3$	COOMe	H	68

Reaction conditions: aryldiazonium tetrachlorozincate double salt: 2.50 mmol; olefin: 5.0 ml; [dbim]Cl: 10 mmol; CuCl: 0.125 mmol; Zn dust: 0.250 mmol; reaction time: 30 min; room temperature.

[a] Isolated yield.

In conclusion, Meerwein reaction was successfully carried out in 'solventless' conditions using a chloride based ionic liquid. The catalytic system comprising of CuCl/Zn in [bdim]Cl allowed to reach satisfactory (and reproducible) results. Yields were fair even for electron-donating substituted diazonium salts, which were notoriously poorly reactive in the Meerwein reaction.

Acknowledgements

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23. Experimental conditions: an open thick walled vessel was charged with IL (10 mmol), olefin (5.0 mL), Zn dust (0.25 mmol) and CuCl (0.125 mmol). Diazonium tetrachlorozincate (2.5 mmol) was added portionwise. After reaction completion (no more gas evolution), water (10 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The organic phase was washed with saturated EDTA solution (2 × 5 mL), dried with Na_2SO_4 and evaporated. The crude was purified by flash chromatography (either petroleum ether–acetone or petroleum ether–ethyl acetate mixtures as eluent) affording the pure product. All runs were repeated at least twice.
24. 3-(4-Acetylaminophenyl)-2-chloro-propionic acid methyl ester: this product was obtained as a white solid, mp 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 2.14 (s, 3H, CH_3CO), 3.22 (ddd, $J = 74.33$ Hz, $J = 14.06$ Hz, $J = 7.30$ Hz, 2H, PhCH_2), 3.73 (s, 3H, CH_3O), 4.22 (t, $J = 7.30$ Hz, 1H, C*H*Cl), 7.14 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.93 (s, 1H, N*H*); ^{13}C NMR (101 MHz, $CDCl_3$): 24.47, 40.47, 52.97, 57.27, 120.10, 129.85, 131.57, 137.30, 168.78, 169.72.