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Ionic liquid as Green solvent for α-alkylation of Active Methyelne Compounds

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Abstract

A selective monoalkylation of active methylene compounds with various alkyl halides in 1-butyl-3-methylimidazolium hexafluorophosphate [bmim] [PF_6] ionic liquid is reported here. The product can be recovered by vacuum distillation and the ionic liquid can be recycled without any loss in yield.

Keywords: Alkylation, phenylacetonitriles, diphenylacetonitrile, ionic liquid, ethyl acetoacetate, diethyl malonate.

Introduction

Organic reactions have been studied in conventional molecular solvents for decades. Release of these volatile organic solvents in the atmosphere causes detrimental effects on environment and human health. In today's environmentally conscious world, the focus is on developing 'greener technologies' that would solve dual purposes, i.e. develop modern techniques, that are not only eco-friendly but also solve the purpose of advancement of science in a truer sense.

Room temperature ionic liquids (RTILs) are a new class of solvent formed by the direct combination of organic cation such as N-alkyl-pyridinium or 1-alkyl-3-methylimidazolium and inorganic anions like haloaluminate, hexafluorophosphate and tetrafluoroborate. With the increasing global demand for developing environmentally safer technology as well as the replacement of VOC's, ionic liquids are gaining immense popularity. This is due to their negligible vapor pressure, non-flammability, unique solvating power and recyclability. Hence, they are rightly considered as 'greener solvents'. Reports show a variety of reactions having been carried out in room temperature ionic liquids ranging from electrophilic reactions[1,2], hydrogenation[3], Wittig reaction[4], heterocyclic synthesis[5,6], to nucleophilic substitution reactions[7,8]. Several reviews on this novel solvent have been reported[9-12].

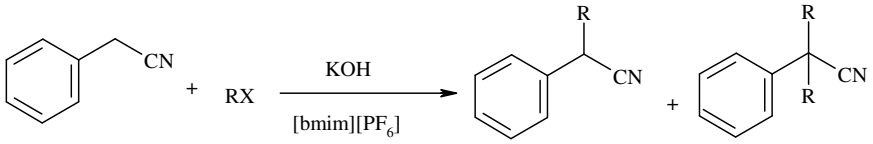
C-C bond formation is an important reaction in organic synthesis. The α-alkylation reaction of phenylacetonitrile is of commercial importance due to the use of the α-alkylated derivatives as pharmaceutical intermediates[13]. Drugs like oxeladine, pentapiperide, phenoperidine, dicyclonine, etc. have been synthesized through alkylation of phenylacetonitrile with various alkyl halides.

Methods for the alkylation of esters and nitriles have been reviewed[14]. These procedures generally involve the use of hazardous and expensive condensing agents like $NaNH_2$, metal hydrides, triphenylmethide, potassium tertiary butoxide, alkoxides, etc, and use of strictly anhydrous organic solvents, ether, benzene, DMF, DMSO, liq. NH_3. These reagents demand an inert atmosphere. Without protection from atmosphere afforded by the solvent vapour or by an inert gas, many of the bases are rapidly attacked by molecular oxygen, resulting in lowering of yields. Besides this, solvents like DMSO and DMF pose general problems of odour as well as the difficulty encountered in separating these solvents from the products. Till date, use of phase transfer catalysts is the simplest method for the alkylation of various active methylene compounds[15].

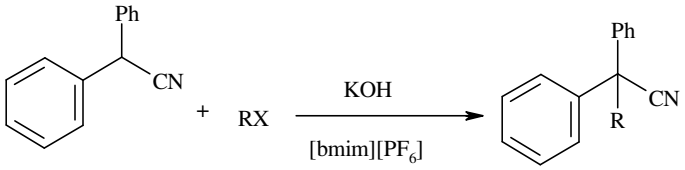
Our continued search for 'greener methods' of synthesis and the established utility of RTILs, as environmentally benign solvents, prompted us to study alkylation of a few active methylene compounds, phenylacetonitrile (1), diphenylacetonitrile (5), ethyl acetoacetate (8) and diethyl malonate (9) with different alkyl halides in 1-butyl-3-methylimidazolium hexafluorophosphate [bmim] [PF_6] ionic liquid using KOH as a base. The [bmim] [PF_6] was prepared by the procedure reported in literature[16]. The results of alkylation of (1) and (5) with different alkyl halides (2) are given in table-1.

Materials and Methods

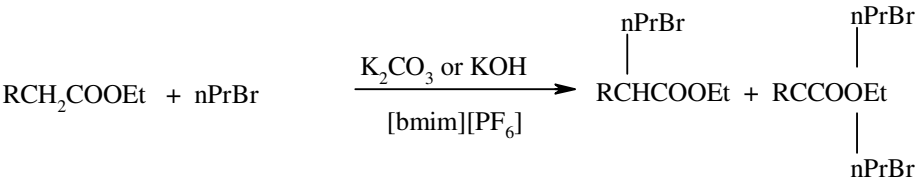
Materials: All the reagents and chemicals were procured from commercial sources (SD Fine Chemicals, India). 1-methylimidazole (Merck-India) was dried, distilled and stored over KOH and ethyl acetate was dried over CaH_2. 1-butyl chloride (Aldrich, USA) was used without further purification. MARS 5 microwave oven digester supplied by CEM Corporation was used for preparation of quaternary salt 1-butyl-3-methylimidazolium chloride[17].



1 2 3a: R = Et 4a: R = Et
R= Et, nPr, 3b: R = nPr 4b: R = Pr
nBu, $PhCH_2$- 3c: R= nBu 4c: R = Bu
X= Br, Cl 3d: R= $PhCH_2$- 4d: R=$PhCH_2$-



5 6 7a: R = Et
R= Et, nPr, allyl 7b: R = nPr
X = Br 7c: R = allyl



8: R = $COCH_3$ 10 11a: R = $COCH_3$ 12a: R = $COCH_3$
9: R = COOEt 11b: R = COOEt 12b: R = COOEt

Scheme-1
Alkylation of active methylene compounds with different alkyl halides in [bmim] [PF_6] ionic liquid

Preparation of 7c: In a typical reaction, diphenylacetonitrile (5) (0.97 g, 5 mmol) was dissolved in 2 ml of [bmim][PF_6] ionic liquid, to it allylbromide (0.73 g, 6 mmol) and KOH (0.56 g, 10 mmol) were added and stirred at 70^0C for 50 min. The reaction mixture was neutralized by adding dil. HCl, followed by extraction with Et_2O and washing twice with H_2O. The Et_2O layer was then passed through sodium sulphate and evaporated. The resultant product was obtained in the pure form, analyzed by GC (SE-30 column on Eshita model with FID and N_2 as gas-carrier) and no further purification was necessary. The ionic liquid was recovered and reused.

Yield 99%, IR (KBr): ν = 2237 cm^{-1} (CN stretching) ; ^{1}H NMR of 7c, (300 MHz, $CDCl_3$): δ = 3.12 (d, 2 H, J=1.08 Hz, C-CH_2), 5.14-5.25 (m, 2H, =CH_2), 5.62 (m, 1H, CH), 7.3- 7.42 (m, 10 H, H_{arom}) ^{1}H NMR of 3a, (300 MHz, $CDCl_3$): δ = 1.06 (t, 3 H, CH_3), 1.93-1.98 (m, 2H, -CH_2), 3.73 (m, 1H, CH), 7.3- 7.4 (m, 5H, H_{arom}).

Note: In case of entries 1-4 (table-1) and 1-2 entries (table-3) the products were purified by column chromatography using $CHCl_3$/ Petroleum-ether (3:2) as the eluent.

Results and Discussion

We observed that with equimolar amount of KOH the reaction did not proceed, it was only with 2 equivalents of KOH that the product formation (monitored on TLC) was observed. Hence, we kept the concentration of KOH in all cases as 2 equivalent. Besides this, solid KOH was present in the system during the entire course of the reaction. This could be attributed to the low nucleophilicity of the ionic liquid-KOH mixture which allows only surface reactivity.

Table -1
Results of alkylation of 1 and 5 in [bmim] [PF_6]

Entry	Substrate	RX	*Time (h)*	*Temp (^0C)*	*Product*	Yield (%)[b]
1.	1	*EtBr*	3.5	40	3a	73[c]
2.	1	*n-PrBr*	1.5	70	3b+4b	84[d]
3.	1	*n-BuBr*	1.7	75-80	3c+4c	75[e]
4.	1	$PhCH_2Cl$	4.5	75-80	3	94
5.	5	*EtBr*	2.5	40	7a[a]	95
6.	5	*n-PrBr*	1	70	7b[a]	100
7.	5	CH_2=$CHCH_2Br$	0.8	70	7c[a]	99

[a]Isolated yields, [b]Yields are based on GC analysis, [c]100 % selectivity of 3a, [d]88 % selectivity of 3b and 12 % 4b, [e]99.7 % selectivity of 3c and 0.3 % 4c

The reaction of 1 with n-PrBr was carried out both at room temperature as well as at 70 ^oC. At both the temperatures the reaction took place, but at rt it took 3.5h to give 62 % 3b and 4.5 % of 4b; whereas at 70 ^oC within 1.5 h 75 % 3b and 9 % of 4b were obtained.

In order to avoid the use of a solvent during the work-up, we carried out a 15 mmol reaction of **1** with n-PrBr under identical conditions. After the reaction was complete, the ionic liquid layer containing the reactants and product was transferred to a micro distillation assembly and the product was vacuum distilled.

To compare the preference of the ionic liquid [bmim][PF_6] with a molecular solvent in the nucleophilic reaction, we carried out the reaction of 1 with 1-BuBr under identical conditions in DMSO, which is highly polar solvent and highly favourable for an nucleophilic substitution reaction. When DMSO was used as a solvent 67 % 3c and 14 % 4c were formed; whereas in the case of ionic liquid 75 % 3c and just 0.2 % 4c were obtained. Though the yields were nearly the same in both the cases, still ionic liquid certainly has an advantage over DMSO as an aprotic polar solvent; since the latter poses general problems of odour, interference in the product isolation, and non- recovery.

The major advantage that ionic liquid offers over other conventional organic solvents is the recyclability (table-2). Ionic liquid could be reused even after 5 cycles. We did not observe any loss in yield of the product nor in the nature of ionic liquid (confirmed by IR and ^1H NMR).

Table -2
Reuse of recovered [bmim] [PF_6] in the reaction of 1 with n-PrBr

Cycles	Combined yield (%)
1	84
2	84
3	84
4	83
5	83

With esters 8 and 9, similar results were obtained with selectivity towards mono alkylated product (table-3).

Table- 3
Results of alkylation of esters 8 and 9 in [bmim] [PF_6] with nPrBr

Entry	Ester[a]	Product	Combined yield (%)[b]	Selectivity (%)	
				Mono-	di-
1	8	11a+12a	73	87	13
2	9	11b+12b	86	68	32

[a]Alkylation of both the esters was carried out at 70 ^oC for 2 h,
[b]Yields are based on GC analysis

Conclusion

In conclusion, we have demonstrated an efficient method of the alkylation of active methylene compounds in [bmim] [PF_6], without the use of a phase transfer catalyst or any dangerous condensing agents. The ionic liquid acts both as solvent as well as catalyst, and hence an excellent substitute for classical aprotic solvent as well as PTC catalyzed alkylation of active methylene compounds. The [bmim] [PF_6] offers the additional benefit of cleaner reaction and solvent recovery. The yields obtained are excellent. Selectivity as well as ease of product isolation by vacuum distillation provides a greener method of synthesis.

Acknowledgement

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References

1. Adams C.H., Earle M.J. Roberts G and Seddon K.R., Friedel-Crafts reactions in room temperature ionic liquids, *J. Chem. Soc., Chem. Commun.*, 2097, (**1998**)

2. Khadilkar B.M and Rebeiro G.L., Benzoylation in room temperature ionic liquids, *Synth. Commun.,* **30**, 1605 (**2000**)

3. Saurez P.A.Z., Dulluis J.E.L., Einloft S., De Souza R.F and Dupont J., The use of new ionic liquids in two-phase

catalytic hydrogenation reaction by rhodium complexes, *Polyhedron*, **15**, 1217 **(1996)**

4. Virginie Le B and Rene G., *J. Chem. Soc., Chem. Commun.*, **22**, 2195 **(2000)**

5. Khadilkar B.M and Rebeiro G.L., Chloroaluminate ionic liquid for Fischer indole synthesis, *Synthesis*, **3**, 370 **(2001)**

6. Khadilkar B.M and Khandekar A.C., Pechmann Reaction in Chloroaluminate Ionic Liquid, *Synlet,* **1**, 152 (**2002**)

7. Earle M.J., McCormac P.B and Seddon K.R., Regioselective alkylation in ionic liquids, *J. Chem. Soc., Chem. Commun.*, 2245 (**1998)**

8. Wheeler C., West K.N., Liotta C.L and Eckert C.A., Ionic liquids as catalytic green solvents for nucleophilic displacement reactions, *J. Chem. Soc., Chem. Commun.*, 887 (**2001**)

9. Ratti R., Use of Non-Conventional Reaction Media: A Green Approach, *Res. J. Chem. Sci.,* **5(3)**, 77-89 **(2015)**

10. Gogoi S., Enzymatic Bioconversion in Non-conventional Media*, Res.J.chem.sci.,* **4(11),** 103-116 **(2014)**

11. Mohd S., Sayyed H. , Sayyed A. , Pradhan V. and Mazahar F., Thermodynamic Characteristics of Solvents: A Review, *Res. J. chem. sci.,* **3(11),** 98-104 **(2013)**

12. Dharaskar S.A., Ionic Liquids (A Review): The Green Solvents for Petroleum and Hydrocarbon Industries, *Res. J. chem. sci.,* **2(8),** 80-85 **(2012)**

13. Starks C.L., Liotta C. L and Halpern M., Phase-transfer catalysis reactions with strong bases. Phase Transfer Catalysis, Chapman and Hall, London, 383 (**1994)**

14. Cope A.C., Holmes H.L and House, H.O., The alkylation of esters and nitriles. Organic Reactions, John Wiley and Sons, New York, **9**, 107 (**1957**)

15. Masamune S., Phase-transfer alkylation of nitriles: α-phenylbutyronitrile, Organic Synthesis, ed., John Wiley and Sons, New York, **55,** 91 **(1976)**

16. Huddleston J.G., Willauer H. D., Swatloski R.P., Visser A.E and Rogers R.D., Room temperature ionic liquids as novel media for 'clean' liquid-liquid extraction, *J. Chem. Soc., Chem. Commun.*, 1765 (**1998)**

17. Khadilkar B.M and Rebeiro G.L., Microwave assisted synthesis of room temperature ionic liquid precursors in closed vessel, *Organic Process Research and Development,* **6(6),** 826 (**2002**)