NJC

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/njc

Potassium Phosphate-Ionic liquid mediated selective *mono*-Michael addition

Anand D Sawant,[a] Surybala D Jagadale,[b] Uday V Desai[b] and Manikrao M Salunkhe[b,c,]*

[a]*Department of Chemistry, Sou. Sushila Danchand Ghodawat Charitable Trust's Group of Institutes, Atigre, Kolhapur, India-416118*

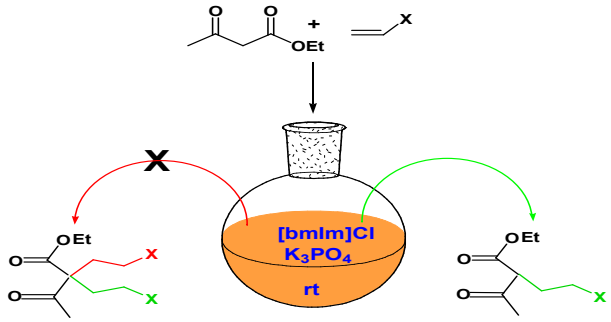
[b] *Department of Chemistry, Shivaji University, Vidhyanagar, Kolhapur, India-416004*

[c]*YCMOU, Nashik, India.*

*E-mail: manikrao.salunkhe@gmail.com,

[a]Email : orgadsawant@gmail.com

A simple and efficient process for exclusive *mono*-Michael addition of active methylene compounds to conjugated esters, nitriles and ketones is developed. Ionic liquid mediated reaction is carried out at room temperature. Reaction carried out at 60°C resulted into double addition product. A mechanism is proposed and supported by P^{31} and DOSY NMR analysis of used ionic liquid.



X= CN, CO_2Me, CO_2Bu-n

Key words: Michael addition, active methylene compounds, ionic liquid, chemo selectivity, potassium phosphate.

NJC

RSCPublishing

LETTER

Potassium Phosphate-Ionic liquid mediated selective *mono*-Michael addition

Cite this: DOI: 10.1039/c3njoooooox

Anand D Sawant, [a] Surybala D Jagadale, [b] Uday V Desai[b] and Manikrao M Salunkhe[b,c,*]

Received oothXXXXX 2013,
Accepted oothXXXXX 2013

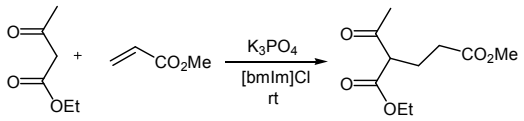
DOI: 10.1039/c3njoooooox

www.rsc.org/njc

A simple and efficient process for exclusive *mono*-Michael addition of active methylene compounds to conjugated esters, nitriles and ketones is developed. Ionic liquid mediated reaction is carried out at room temperature. Reaction carried out at 60°C resulted into double addition product. A mechanism is proposed and supported by P^{31} and DOSY NMR analysis of used ionic liquid.

The conjugate addition of nucleophilic species to α-β-unsaturated systems, commonly known as Michael addition[1] is a fundamental concept in organic chemistry and is considered as one of the most versatile methods in organic synthesis. This reaction is conventionally catalyzed by strong bases that often lead to undesirable side reactions.[2] To date, reagents, such as ruthenium complex,[3] enamines,[4] nanoparticles of silica,[5] metal triflates[6] etc have been reported as catalysts for the Michael addition of active methylene compounds to conjugated carboxylic esters, nitriles, and ketones. Apart from these reports the reaction is extensively investigated.[7] Ranu *et al.* reported a dramatic effect of ionic liquid (IL) on progress of Michael reaction.[8] The vinyl ketones and chalcones gave *mono* addition products while unsaturated esters and nitriles gave *bis*-addition products. To the best of our knowledge selective *mono*-Michael addition is very less investigated.[9] However most of the reported methods suffer from low selectivity, low reaction temperature and use of specially prepared catalysts. Herein we report the exclusive *mono*-Michael addition of various active methylene compounds to conjugated esters and nitriles, catalyzed by potassium phosphate in ionic liquid [bmIm] Cl at room temperature.

Inspired from some earlier investigations,[10] it was decided to study the use of ionic liquids and easily available catalysts for exclusive *mono*-Michael addition. As controlled deprotonation of active methylene compound is the key motif for selective *mono*-Michael addition, it was decided to use easily available mild basic salts in combination with neutral ionic liquid [bmIm]Cl. To optimize reaction conditions, addition of ethyl aceto aetate (EAA) on methyl acrylate was selected as model reaction. The ionic liquid-potassium phosphate mixture was stirred at elevated temperature (60°C) for extended hours (2 h) and then the reaction was carried out at room temperature. To our delight it was found that the reaction of EAA and methyl acrylate was going smoothly in presence of potassium phosphate resulting into exclusive mono addition product. The results are summarized in **Table 1**. It clearly depicts that the potassium phosphate is a most suitable salt to bring about the reaction. On the other hand, the reaction catalyzed by basic ionic liquid [bmIm]OH, results into double addition and there was no any trace of mono addition product. As expected the reaction without catalyst did not show progress.



Sheme 1: Selective *mono*-Michael addition

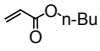
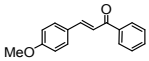
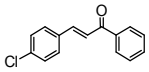
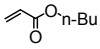
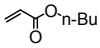
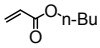
Table 1: Basic salts studied for Selective *mono*-Michael addition

Entry	Salt	Solvent	Yield%[a]
1	K_3PO_4	[bmIm]Cl	95
2	K_2CO_3	[bmIm]Cl	27
3	Na_2CO_3	[bmIm]Cl	18
4	$CaCO_3$	[bmIm]Cl	19
5	-	[bmIm]Cl	No reaction
6	[bmIm]OH	-	0
7	K_2CO_3	THF	20
8	K_3PO_4	THF	34

The mixture of [bmIm]Cl (200 mg) and base (100 mg) was stirred at 60°C for 2hrs and allowed to cool. To this mixture EAA (2mmol) and methyl acrylate (2.2 mmol) was added and stirred at RT for 2 h; [a] GC yields for *mono* –addition product.

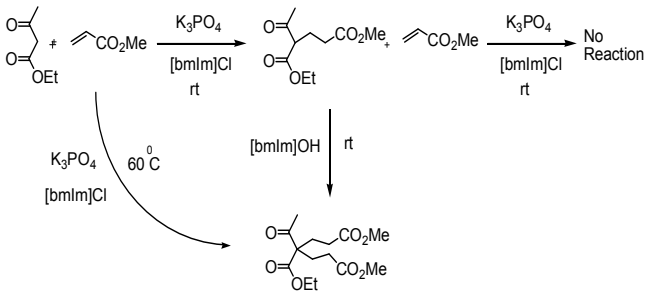
To generalize the protocol, reaction was carried out with wide ranging substrates including chalcones and cyclic keto ester. The results are summarized in Table 2. All reactions proceeded smoothly with reaction time ranging from 2-6 hours. Amongst the active methylene compounds used, nitriles were found to be reacting at relatively slower rate. The reaction of chalcones and cyclic ketoester took relatively longer time to go to completion. Acyclic allyl ketones showed reluctance and there was no any reaction.

Table 2: Potassium Phosphate-[bmIm]Cl mediated *mono*-Michael addition

Entry	Adduct	Acceptor	Time (h)	Yield%[a]
1			2	91
2			2	88
3			2	91
4			3	88
5			6	90
6			6	92
7			3	91
8			3	88
9			3	90
10			4	88
11			4	90
12			5	89
13			5	85
14			5	84
15			4	88

The mixture of [bmIm]Cl (200 mg)and K_3PO_4 (100 mg) was stirred at 60°C for 2hrs and allowed to cool. To this mixture EAA (1mmol) and methyl acrylate (1.2 mmol) was added and stirred at RT; [a] Isolated yields.

In further investigation, the mono addition product was isolated and used as substrate for another addition of methyl acrylate under same reaction conditions. The reaction did not show any progress and the mono addition product remained intact. To explore the effect of temperature, the reaction was carried out at elevated temperature (60°C) and it was resulted into exclusive double addition product (**Scheme 2**). This clearly depicts that there is exclusive mono addition, when reaction is carried out at room temperature.



Sheme 2: Selective *mono*-Michael addition

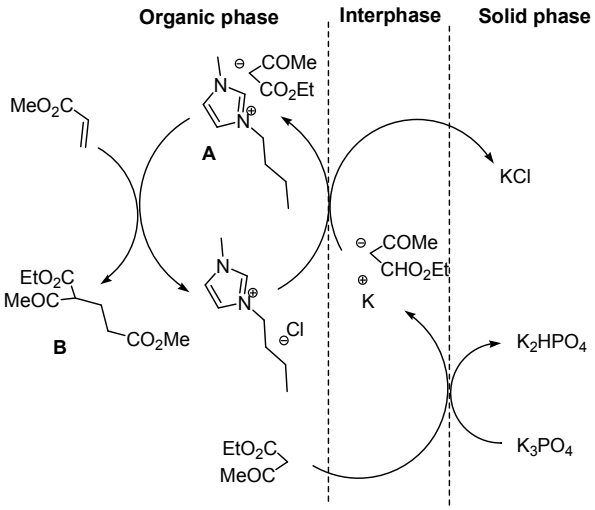
The reusability of catalyst is important from commercial point of view. The reusability of the system was tested using EAA and methyl acrylate as substrates. The potassium phohphate ionic liquid system, after extraction of product in diethyl ether, could be recycled for three times without any substantial loss of catalytic activity.

Table 3: Reusability of the IL- K_3PO_4 system

Cycle	Yield%[a]
1	96
2	91
3	88
4	78

[a] **GC yields**

Earlier report[11] suggested that there is a possibility of existence of ion pair of organic anion and quaternary ammonium cation in organic phase. Based on the assumption and a recently reported[12] mechanism of a potassium phosphate catalyzed reaction, we propose a plausible mechanism for present protocol (Scheme 3).



Scheme 3: Plausible Mechanism

In reaction mixture, there is existence of organic phase, solid phase and interphase. The substrates and ionic liquid remains in organic phase. While the potassium phosphate remains in solid phase. Phosphate is acting as base, and abstract proton from active methylene compound. The active methylene compound is deprotonated in the interphase of organic liquid phase and solid phase. The organic anion enter into organic phase by exchange reaction with anion of ionic liquid [bmIm]Cl. It forms an ion pair (A) of imidazolium cation and organic anion. The anion reacts with methyl acrylate to give mono-Michael addition product (B)**.** Formation of ion pair is the key step in the reaction.

Owing to steric effects further deprotonation of mono addition product (B) becomes cumbersome. Also due to bulky nature, formation of ion pair of imidazolium cation and anion of mono addition product (B) is difficult. This can be the probable reason of exclusive mono-Michael addition reaction. To support this mechanism we carried out P^{31} and DOSY NMR (Figure 1) analysis of isolated ionic liquid. The probability of metathesis reaction between potassium phosphate and ionic liquid [bmIm]Cl is completely warded off due to absence of peak in P^{31} NMR. Peaks and diffusion constant values in the DOSY NMR analysis of fresh and isolated ionic liquid remain unchanged. This clearly depicts that the ionic liquid do not undergo any structural changes. It remains intact and work only as facilitator.

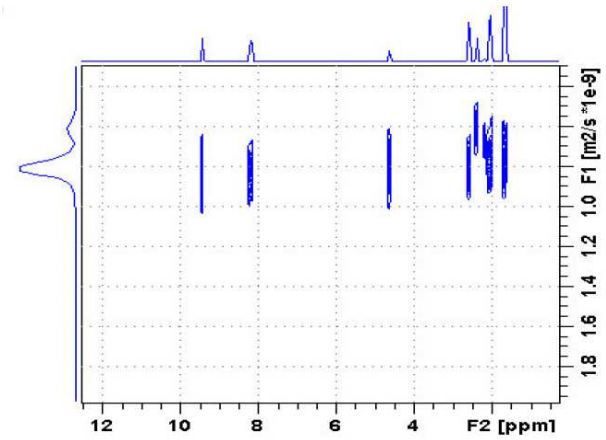


Figure 1: DOSY NMR analysis of used ionic liquid

In conclusion, we have developed a potassium phosphate-ionic liquid catalyzed method for selective *mono*-Michal addition of active methylene compounds on acrylic esters and acrylonitriles. We have proposed a mechanism for the reaction based upon some earlier findings. The mechanism is supported by P^{31} and DOSY NMR analysis of ionic liquid. The difficulty of existence of bulky ion pair of imidazolium cation and anion of mono addition product is a possible reason behind exclusive mono addition. Further investigations are currently under way in our laboratories.

Experimental

General procedure for the preparation of [bmIm]Cl: A mixture of 50 mmol of 1-methylimidazole and 200 mmol of 1-chlorobutane in 6 ml dried toluene was refluxed under nitrogen atmosphere for 24 h to obtain a viscous liquid forming the lower layer. The reaction mixture was cooled to 0^0C and stirred overnight to yield the solid quaternary salt [bmim]Cl (1-butyl-3-methylimidazolium chloride). The excess unreacted 1-haloalkane and toluene were decanted and the salt was washed with diethyl ether (3 x 5 ml). The salt was further purified by recrystallization from acetonitrile / ethyl acetate to yield the product.

General procedure for Michael addition: A mixture of 200 mg of [bmIm]Cl and 100 mg of K_3PO_4 were stirred at 60^0C for 2 hours and then allowed to cool to room temperature. To this mixture , 2mmol of EAA and 2.2 mmol of methyl acrylate was added and stirred at room temperature. After completion of reaction (GC), diethyl ether was added (2X10 ml) and stirred. The separated ether layer was dried over sodium sulphate and solvent was evaporated to get crude product. It was further purified by column chromatography.

Procedure for recyclability: After completion of reaction, the reaction mixture was extracted with diethyl ether (3X30 ml). The potassium phosphate-ionic liquid left in the reaction vessel was dried inder vacuum (3 h). The dried system was used for the next run.

Acknowledgment

MMS is thankful to Department of Science & Technology (DST), New Delhi, and ADS is thankful to Shivaji University, Kolhapur for the financial support.

Notes and references

[a]Department of Chemistry, Sou. Sushila Danchand Ghodawat Charitable Trust's Group of Institutes, Atigre, Kolhapur, India-416118
E-mail: orgadsawant@gmail.com
[b] Department of Chemistry, Shivaji University, Vidhyanagar, Kolhapur, India-416004
[c]YCMOU, Nashik, India.
Fax: (91-231) 2691533
*E-mail: manikrao.salunkhe@gmail.com

1. E. R. Jarvo, S. J. Miller, *Tetrahedron* 2002, **58**, 2481.
2. S. Sulzer-Mosse, A. Alexakis, *Chem. Comm.* 2007, **30**, 3123.
3. S. G. Alvarez, S. Hasegawa, M. Hirano, S. Komiya, *Tetrahedron Lett.* 1998, **39**, 5209.
4. G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, R. Terrel, *J. Am. Chem. Soc.* 1963, **85**, 207.
5. S. Banerjee, S. Santra, *Tetrahedron Lett.* 2009, **50**, 2037.
6. J. S. Yadav, B. V. S. Reddy, G. Baishya, A. V. Narsaiah, *Chem. Lett*. 2005, **34,** 102.
7. (a) C. Gimbert, M. Lumbierres, C. Marchi, M. Moreno-Manas, R. M. Sebastian, A. Vallribera, *Tetrahedron* 2005, **61,** 8598; (b) G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, R. Terrel, *J. Am. Chem. Soc.* 1963, **85,** 207; (c) B. C. Ranu, M. Shah, S. Bhar, *Synth. Commun.* 1997, **27(4),** 621; (d) D. Bensa, T. Constantieux, J. Rodiguez, *Synthesis* 2004, 923; (e) S. Shirakawa, S. Shimizu, *Synlett.* 2007, 3160.
8. B. C. Ranu, S. Banerjee, *Org. Lett.* 2005, **7,** 3049. (b) B. C. Ranu, S. Banerjee, R. Jana, *Tetrahedron* 2007**, 63,** 776.
9. M. R. Saidi, N. Aziz, E. Akbari, F. Ebrahimi,. *J. Mol. Catal. A: Chemical* 2008, **292,** 44; (b) K. Ko, K. Nakano, S. Watanabe, Y. Ichikawa, H. Kotsuki, *Tetrahedron Lett.* 2009, **50**, 4025.
10. S. J. Nara, J. R. Harjani, M. M. Salunkhe, *J .Org. Chem* 2001, **66,** 8616; (b) A. D. Sawant, D. G. Raut, N. B. Darvatkar, U. V. Desai, M. M. Salunkhe, *Catal. Commun.* 2010**, 12,** 273; (c) U. V. Desai, P. D. Pore, R. B. Mane, P. P. Wadgaonkar, *Synth. Commun.* 2004, **34**, 25. (d) K. Ebitani, K. Motokura, K. Mori, T. Mizugaki, K. Kaneda, *J. Org. Chem.* 2006**, 71**, 5440.
11. M. Makosza, M. Fedorynski, *Catal. Rev.* 2003, **45**, 321.

12. N. Qafisheh, S. Mukhopadhyay, A. V. Joshi, Y. Sasson, G. K. Chuah, S. Jaenicke, *Ind. Eng. Chem. Res.* 2007, 46, 3016.

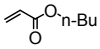
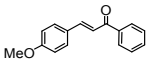
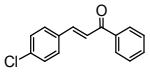
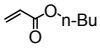
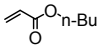
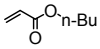
Table of Contents

Table 1: Basic salts studied for Selective *mono*-Michael addition

Entry	Salt	Solvent	Yield%[a]
1	K_3PO_4	[bmIm]Cl	95
2	K_2CO_3	[bmIm]Cl	27
3	Na_2CO_3	[bmIm]Cl	18
4	$CaCO_3$	[bmIm]Cl	19
5	-	[bmIm]Cl	No reaction
6	[bmIm]OH	-	0
7	K_2CO_3	THF	20
8	K_3PO_4	THF	34

The mixture of [bmIm]Cl (200 mg) and base (100 mg) was stirred at 60°C for 2hrs and allowed to cool. To this mixture EAA (2mmol) and methyl acrylate (2.2 mmol) was added and stirred at RT for 2 h; [a] GC yields for *mono* –addition product.

Table 2: Potassium Phosphate-[bmIm]Cl mediated *mono*-Michael addition

Entry	Adduct	Acceptor	Time (h)	Yield%[a]
1			2	91
2			2	88
3			2	91
4			3	88
5			6	90
6			6	92
7			3	91
8			3	88
9			3	90
10			4	88
11			4	90
12			5	89
13			5	85
14			5	84
15			4	88

The mixture of [bmIm]Cl (200 mg)and K_3PO_4 (100 mg) was stirred at 60°C for 2hrs and allowed to cool. To this mixture EAA (1mmol) and methyl acrylate (1.2 mmol) was added and stirred at RT; [a] Isolated yields.

Table 3: Reusability of the IL- K_3PO_4 system

Cycle	Yield%[a]
1	96
2	91
3	88
4	78

[a] GC yields