The Knoevenagel condensation between ethyl 4-chloroacetoacetate and aromatic aldehydes in ionic liquids

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INTRODUCTION

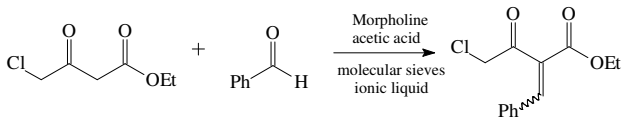
The Knoevenagel condensation is an important C=C bond formation in organic synthesis. Among possible solvents, refluxing benzene or toluene are common choices,[1] and removal of water from the reaction medium is typically done by means of a Dean-Stark trap. To avoid the use of hazardous organic solvents and relatively high temperatures, we were interested in the use of ionic liquids as potential solvents for this condensation.

In the course of our studies towards the synthesis of chiral halogenated β-hydroxyesters, we were particularly interested in the reaction between ethyl 4-chloroacetoacetate and different aromatic aldehydes to produce the corresponding 2-chloroacetyl-3-arylpropenoates.

RESULTS AND DISCUSSION

In order to determine the best reaction conditions, we varied the concentration of the reagents, the catalyst percentage and the nature of the ionic liquid. The yields corresponding to each reaction condition can be seen in Table 1.

Table 1. Reaction yields for the Knoevenagel condensation between benzaldehyde and ethyl 4-chloroacetoacetate.[a]



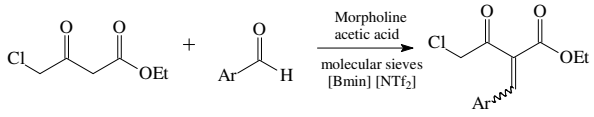
1 2a 3a

Entry	Ionic liquid	Concentration of 2a (mol L^{-1})[b]	Catalyst (mol%)	3a Yield (%)[c]
1	[bmim(PF_6)]	1.0	10	52
2		1.0	20	60
3		2.0	10	66
4		2.0	20	61
5	[bmim(NTf_2)]	2.0	10	75
6		2.0	20	55

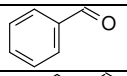
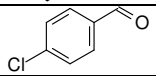
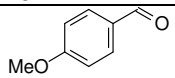
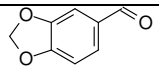
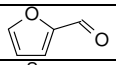
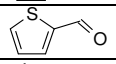
[a] Reactions were carried out on a 2 mmol scale. [b] Aldehyde concentration; 1.2 equivalent of **1** was used. [c] Isolated yield of the E/Z isomers mixture, after column chromatography.

Thus, [bmim(NTf_2)] was the solvent of choice for the condensation, and Entry 5 conditions were used in the reaction with other aromatic aldehydes. The yields for each reaction, as well as the E/Z ratio can be seen in Table 2.

Table 2. Reaction time, yield, and diastereomeric ratio (d.r.) for the Knoevenagel condensation between ethyl 4-chloroacetoacetate and different aromatic aldehydes.[a]



1 2a-f 3a-f

Aldehyde	Reaction time (h)	Yield (%)	d.r. (E:Z)
a 	1.0	75	73:27
b 	1.5	57	56:44
c 	2.0	67	59:41
d 	1.5	82	85:15
e 	0.5	84	69:31
f 	1.0	44	66:34

[a] Reactions were carried out on a 2 mmol scale. [b] Isolated yield of the E/Z isomers mixture, after column chromatography. [c] Determined by ^{1}H NMR of the crude mixture.

CONCLUSION

The Knoevenagel condensations between ethyl 4-chloroacetoacetate and different aromatic aldehydes were successfully carried out in [bmim(PF_6)] and [bmim(NTf_2)], affording the corresponding 2-chloroacetyl-3-arylpropenoates in moderate to high yields.

ACKNOWLEDGEMENTS

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REFERENCES

[1] Pullabhotla, V. S. R. R., Rahman, A., Jonnalagadda, S. B. *Catal. Commun.* **2009**, *10*, 365-369.