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Tetrahedron Letters 45 (2004) 1427–1431

Tetrahedron Letters

Efficient nucleophilic substitution reactions of highly functionalized allyl halides in ionic liquid media

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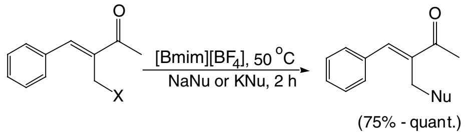
Received 5 November 2003; revised 4 December 2003; accepted 10 December 2003

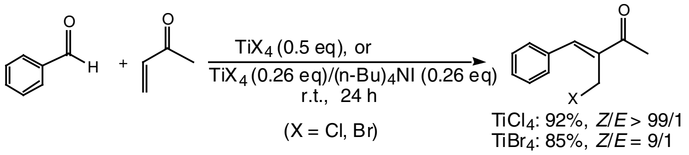
Abstract—Nucleophilic substitution reactions of highly functionalized allyl halides with three anions, N_3^-, AcO^-, and $PhSO_2^-$, in ionic liquid media were conducted. The ionic liquid, [Bmim][BF_4], was found to be superior to classical organic solvents to give higher yields and faster reaction rates. The resulting products belong to multifunctionalized trisubstituted α,β-unsaturated ketones, which are useful building blocks for organic synthesis.

Recently, we developed a highly efficient approach to mutiple-functionalized (*Z*)-keto allyl bromides and chlorides.[1] The reaction was conveniently carried out through a one-pot tandem difunctionalization of α,β-unsaturated ketones mediated by a nonstoichiometric amount of titanium(IV) halides (TiX_4, X = Cl and Br) or by the combination of $TiX_4/(n\text{-Bu})_4NI$[2] in highly stereoselective fashions (Scheme 1). In this communication, we describe the S_N2 nucleophilic substitution reactions using these (*Z*)-keto allyl substrates with three anions, N_3^-, AcO^-, and $PhSO_2^-$ to further extend the scope of the above new process. Both normal organic solvents and an ionic liquid were utilized for the reaction. We found that when the ionic liquid, [Bmim]-[BF_4] (butylmethylimidazolium tetrafluoroborate), was employed as the media the chemical yields were higher than those in normal organic solvents. In the meanwhile, the reaction proceeded at a faster rate (Scheme 2).



Scheme 2.

As compared with normal organic solvents, ionic liquids (IL) as reaction media have several attractive properties for chemical transformations.[3,4] These properties include nonvolatility, noncombustibility, and dissolvability of polar compounds. Ionic liquids can be easily recycled, and therefore, are environmentally friendly. In fact, the ionic liquid-based organic synthesis has become an active topic in organic chemistry in the past several years. Very recently, Kabalka et al. reported the synthesis of substituted allyl acetate and sulfones[5] via S_N2' reactions of the Morita–Baylis–Hillman (MBH)



Scheme 1.

Keywords: α,β-Unsaturated ketone; Ionic liquid; S_N2 reaction; Halides.

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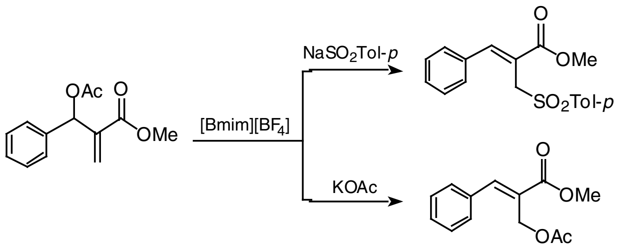
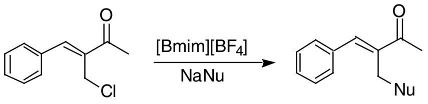
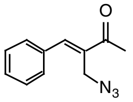
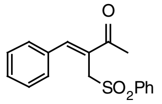
doi:10.1016/j.tetlet.2003.12.051



Scheme 3.

Table 2. Comparative results with NaN_3 and $NaSO_2Ph$ as nucleophiles



Product	Nu^-	DMF	IL
	NaN_3	81%	98%
	$NaSO_2Ph$	68%	75%

adducts[6] in ionic liquid media with great success (Scheme 3). Their interesting work promoted us to carry out the present work presented in this report.

Initially, we carried out the model study using a (*Z*)-keto allyl chloride as the substrate and with KOAc as nucleophile in different normal solvents and in [Bmim][BF_4] (Table 1). As anticipated, only DMF and ionic liquid gave good yields for S_N2 products. At the same time, the later resulted in much higher chemical yield (92%) than DMF (77%). TLC monitoring showed that the reaction was complete within the period of 2 h, whereas, it took 24 h to be finished in DMF. Similar observations were encountered for the reaction of this substrate with two other nucleophiles, N_3^- and $PhSO_2^-$. The yields are summarized in Table 2.

We therefore have carried out the S_N2 nucleophilic substitutions on different substrates (seven chlorides and one bromide) with the above three nucleophile salts in ionic liquid. For the 24 cases shown in Table 3, nearly all of them gave excellent yields within the reaction period of 2 h. Similar to Kabalka's S_N2' reactions of the Morita–Baylis–Hillman adducts in the same ionic liquid media where 1.5 equiv of nucleophiles was used, 1.3 equiv of nucleophiles was enough to finish the current S_N2 reactions and to achieve the optimized chemical yields. The products are very convenient to purify either through column chromatography for oils or recrystallization for solids.

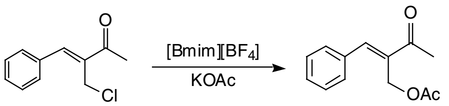
As revealed by Table 3, the bromide substrate (cases 4–6) did not show the obvious advantage over its chloride counterparts for the reaction in both yield and reaction rate. In fact, with NaN_3 and KOAc nucleophiles the chloride even gave similar yields (98% and 92%, respectively) to that of the bromide (90%). However, a little higher yield from bromide (81%) than the chloride substrate (75%) was obtained when $PhSO_2Na$ was used as the nucleophile. It should be pointed out that the last three products (**19**–**22**) are particularly useful for organic synthesis because of their diene functionality.

There are no S_N2' reaction products observed at all for all 24 cases. This is due to the β-substituents on these substrates to give steric effects. For diene cases, the additional stability of the conjugate system can also make the possible S_N2' reaction difficult under the present conditions.

The similar substitution reactions by using other nucleophiles such as NaCN, NaSAr, and NaSePh, will be studied in our laboratories. The resulting products will be subject to the aminohalogenation and electrophilic diamination reactions in future.

In summary, a series of new multifunctionalized allyl azides, acetates, and sulfones have been efficiently synthesized by using ionic liquid, [Bmim][BF_4], as the reaction media, which is superior to classical organic solvents for both chemical yields and reaction rates. The resulting products belong to trisubstituted α,β-unsaturated ketones, which are versatile building blocks for organic synthesis.

Table 1. Results of different solvents with KOAc as the nucleophile



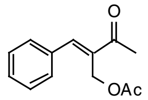
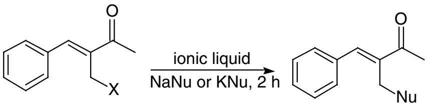
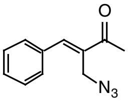
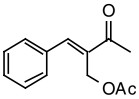
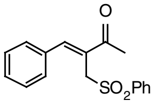
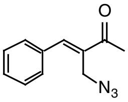
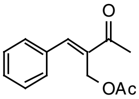
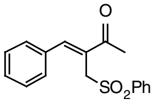
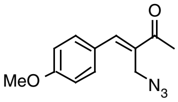
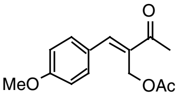
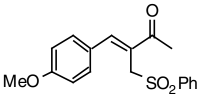
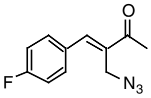
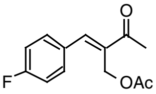
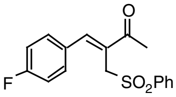
Product	DMF (time)	THF	DCM	Dioxane	IL (time)
	77% (24 h)	No reaction	No reaction	5%	92% (2 h)

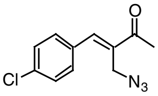
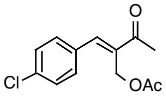
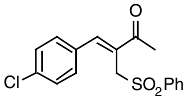
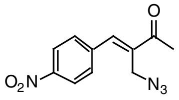
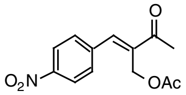
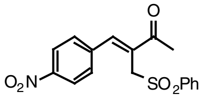
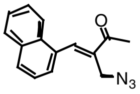
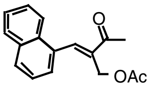
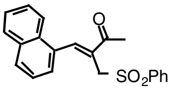
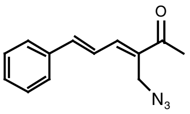
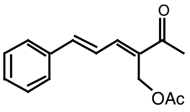
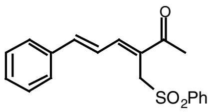
Table 3. Yields of substitution reactions of various substrates in ionic liquid [Bmim][BF_4][7,8]



Entry	Product		NaNu/KNu	Yield (%)	Mp (°C)
1		**1**	NaN_3	98	Oil
2		**2**	KOAc	92	Oil
3		**3**	$NaSO_2Ph$	75	Oil
4	 (from bromide substrate)	**1**	NaN_3	90	Oil
5	 (from bromide substrate)	**2**	KOAc	90	Oil
6	 (from bromide substrate)	**3**	$NaSO_2Ph$	81	Oil
7		**4**	NaN_3	88	Oil
8		**5**	KOAc	94	129
9		**6**	$NaSO_2Ph$	87	140–141
10		**7**	NaN_3	88	55–57
11		**8**	KOAc	Quant.	64–65
12		**9**	$NaSO_2Ph$	Quant.	148–149

(*continued on next page*)

Table 3 (*continued*)

Entry	Product		NaNu/KNu	Yield (%)	Mp (°C)
13		**10**	NaN_3	83	72
14		**11**	KOAc	Quant.	86–88
15		**12**	$NaSO_2Ph$	90	98–101
16		**13**	NaN_3	89	100–101
17		**14**	KOAc	89	129
18		**15**	$NaSO_2Ph$	80	140–141
19		**16**	NaN_3	90	Oil
20		**17**	KOAc	94	Oil
21		**18**	$NaSO_2Ph$	Quant.	Oil
22		**19**	NaN_3	91	89–90
23		**20**	KOAc	94	126–130
24		**21**	$NaSO_2Ph$	98	157–160

Acknowledgements

We gratefully acknowledge the National Institutes of Health (CA 99995-1) and the Robert A. Welch Foundation (D-1361, D-1460) for the generous support of this work, the National Science Foundation (CHE-9808436) for partial funding of the 500 MHz NMR spectrometer.

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5. Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2003**, *44*, 4673–4675.
6. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Patra, A.; Roy, A. K.; Joshi, B. S.; Roy, R.; Batra, S.; Bhaduri, A. P. *Tetrahedron* **2003**, *59*, 663–670; (c) Aumann, R.; Fu, X. L.; Holst, C.; Fröhlich, R. *Organometallics* **2002**, *21*, 4356–4368; (d) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507–4510; (e) Pathak, R.; Shaw, A. K.; Bhaduri, A. P. *Tetrahedron* **2002**, *58*, 3535–3541; (f) Iwamura, T.; Fujita, M.; Kawakita, T.; Kinoshita, S.; Watanabe, S.; Kataoka, T. *Tetrahedron* **2001**, *57*, 8455–8462.
7. The synthesis of starting materials were conducted by following our published procedure as described in Ref. 1.
8. Typical procedure for the S_N2 nucleophlilic substitution reactions: Into a vial was loaded the substrate (0.51 mmol, 1.0 equiv) and ionic liquid (400 mg). The resulting mixture was stirred for 10 min and followed by the addition of the nucleophile (0.65 mmol, 1.3 equiv). The mixture was stirred at 45–50 °C for 2 h, and then cooled to room temperature. The product was extracted with diether ether (3 × 10 mL). The crude product is finally purified by silica column chromatography with EtOAc/hexane (4/1 v/v) as the eluent.