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Amberlite IRA900N$_3$ as a New Catalyst for the Azidation of α,β-Unsaturated Ketones under Solvent-Free Conditions

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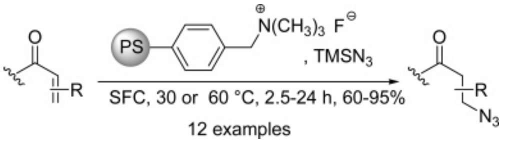
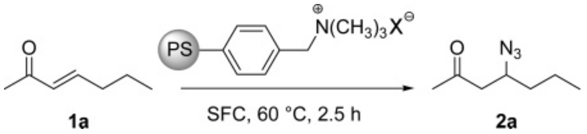


Amberlite IRA900N$_3$ is an excellent organocatalyst for the azidation of α,β-unsaturated ketones with trimethylsilyl azide under solvent-free conditions. By avoiding the use of metallic species and of the organic reaction medium, the procedure is a green tool for the preparation of β-azido ketones under mild conditions with yields from good to excellent. The catalyst can be recovered and re-used with no loss of its efficiency.

β-Amino carbonyl compounds are versatile intermediates for the synthesis of antibiotics, fine chemicals, pharmaceuticals, and natural products.[1]

Despite the large number of practical applications, efficient procedures for their preparation are currently limited. The most direct and widely employed method involves the conjugated addition of a N-nucleophile (e.g., N_3^-) to α,β-unsaturated ketones by using a base or an acid as a catalyst and performing the addition in an organic solvent,[2] water,[3] or an ionic liquid.[4] To avoid the use of the highly toxic and explosive hydrazoic acid, an excellent protocol using a combination of trimethylsilyl azide (TMSN$_3$) and acetic acid as the azido ion source and a solid-supported alkyl imidazole as a catalyst in dichloromethane (DCM) has been reported.[5]

TABLE 1. Optimization of the Azidation of 1a under SolFC at 60 °C



entry	medium	AmberliteX (molar equiv)	TMSN$_3$ (molar equiv)	yield of **2a**[a] (%)
1	SolFC		1.1	traces
2	SolFC	F (0.1)	1.1	90
3	MeCN	F (0.1)	1.1	75
4	DCM	F (0.1)	1.1	84
5	SolFC	N$_3$ (1.1)		
6	MeCN	N$_3$ (1.1)		
7	SolFC	N$_3$ (0.1)	1.1	90

[a] Isolated yield.

Our research is devoted to the development of a green organic synthesis by investigating the use of water[6] and solvent-free conditions (SolFC)[7] as a valid alternative to the use of volatile and toxic organic solvents. Accordingly, we are exploring the use of polymer-supported organocatalysts under SolFC. We have recently reported that polystyrene-supported 1,3,4,6,7,8-hexahydro-2*H*-pirimido[1,2-*a*]-pyrimidine is an efficient basic Brønsted catalyst for many organic transformations under SolFC.[7a]

According to these results, we believe that the use of polymer-supported organocatalysts under SolFC is a promising strategy to increase the chemical efficiency and to minimize the environmental cost of the organic synthesis.

We have decided to investigate an alternative synthesis of β-azido ketones **2a**−**l** starting from α,β-unsaturated ketones **1a**−**l**. We have planned to realize this project by using polymer-supported organocatalysts and byperforming the process in the absence of an organic solvent (SolFC).

Considering the fact that we have already showed that tetrabutylammonium fluoride (TBAF) is an excellent catalyst for the activation of TMSN$_3$ both as trimethylsilyl and as azido ion sources,[8] we have envisaged that polystyrene-supported

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(1) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070. (b) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. (c) Tramontini, M.; Angiolini, L.; *Tetrahedron* **1990**, *46*, 1791−1837.

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(3) Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Zhou, S.-L. *Synlett* **2003**, 2246−2248.

(4) Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Zhou, S.-L. *Tetrahedron Lett.* **2004**, *45*, 1219−1221.

(5) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107−1109. Other protocols using TMSN$_3$ are (a) Adamo, I.; Benedetti, F.; Berti, F.; Campaner, P. *Org. Lett.* **2006**, *8*, 51−54. (b) Dondoni, A.; Marra, A.; Boscarato, A. *Chem.*−*Eur. J.* **1999**, *5*, 3562−3572. (c) Dondoni, A.; Boscarato, A.; Marra, A. *Tetrahedron: Asymmetry* **1994**, *5*, 2209−2212. (d) Thiergardt, R.; Rihs, G.; Hug, P.; Peter, H. H. *Tetrahedron* **1995**, *51*, 733−742.

(6) As representative examples see: (a) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *67*, 2315−2321. (b) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Org. Lett.* **2005**, *7*, 4411−4414. (c) And literature cited herein.

(7) As representative examples see: (a) Fringuelli, F.; Pizzo, F.; Vittoriani, C.; Vaccaro, L. *Chem. Commun.* **2004**, 2756−2757. (b) Fringuelli, F.; Pizzo, F.; Vittoriani, C.; Vaccaro, L. *Eur. J. Org. Chem.* **2006**, 1231−1236. (c) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Zuccaccia, C.; Vaccaro, L. *Green Chem.* **2006**, *8*, 191−196. (d) Fringuelli, F.; Girotti, R.; Pizzo, F.; Zunino, E.; Vaccaro, L. *Adv. Synth. Catal.* **2006**, *348*, 297−300. (e) Fringuelli, F.; Girotti, R.; Pizzo, F.; Vaccaro, L. *Org. Lett.* **2006**, *8*, 2487−2489. (f) And literature cited herein.

(8) (a) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 6734−6737. (b) Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2896−2898. (c) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6526−6529. (d) D'Ambrosio, G.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2005**, *7*, 874−877.

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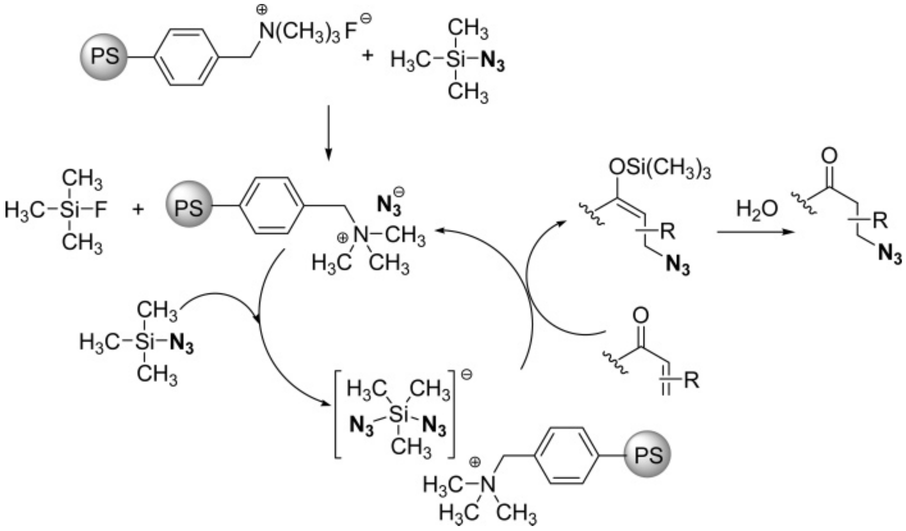
SCHEME 1. Mechanism of the Azidation of α,*β*-Unsaturated Ketones in the Presence of Amberlite IRA900F



ammonium fluoride (Amberlite IRA900F)[9] could be conveniently used as an anionic activator of the silicon−nitrogen bond of $TMSN_3$.

(3*E*)-Hept-3-en-2-one (**1a**) was chosen as a representative enone to study the optimization of the process.

Azidation of **1a** with $TMSN_3$ in the absence of a catalyst gave only traces of **2a** (Table 1, entry 1). In the presence of 1.1 equiv of $TMSN_3$ and 0.1 equiv of Amberlite IRA900F, the conversion of **1a** was complete in 2.5 h under SolFC at 60 °C giving the desired product **2a** in a 90% yield (Table 1, entry 2). Poorer results were obtained when the same reaction was performed in MeCN or DCM (Table 1, entries 3 and 4).

At the end of the process under SolFC, the solid catalyst was recovered and re-used in four more runs obtaining the same results in terms of reaction time and isolation yield of **2a**. Surprisingly, despite its unchanged efficiency, the solid catalyst recovered after the first run did not contain fluoride ions anymore, as shown by fluorimetric analysis. Elemental analysis of the recovered material showed an increase in the percentage of nitrogen atoms, whichwas in agreement with an Amberlite polymer where azide ions have replaced the fluoride ones. Therefore, the recovered material was Amberlite IRA900N$_3$.

We, therefore, prepared independently Amberlite IRA900N$_3$, which is not commercially available, starting from the corresponding Amberlite IRA900F or IRA900Br via exchange of the anion by using a 5 M NaN_3 aqueous solution.

Azidation of **1a** did not occur at all when Amberlite IRA900N$_3$ was used in an over-stoichiometric amount in the absence of $TMSN_3$, both under SolFC and in MeCN (Table 1, entries 5 and 6). On the contrary, when $TMSN_3$ (1.1 molar equiv) was used, Amberlite IRA900N$_3$ (0.1 molar equiv) proved to be as effective as Amberlite IRA900F (Table 1, entry 7 vs entry 2).

These results have been tentatively explained by the mechanism illustrated in Scheme 1.

Initially, there is a fast exchange reaction within Amberlite IRA900F and $TMSN_3$ with the formation of Amberlite IRA900N$_3$. Then, the azido ion bonded to the resin acts as a Lewis base coordinating the silicon atom to form a pentavalent azido silicate species where the azido ion is sufficiently activated to attack the enone and give the corresponding adduct which is readily hydrolyzed by atmospheric humidity to the corresponding *β*-azido ketone.

In addition, we have also used the Amberlite IRA400N$_3^-$ form, which is commercially available, but unsatisfactory results were obtained proving that the nature of the polymer support plays a central role for the efficiency of the catalyst.[10]

We have then confirmed the efficiency of our protocol by extending the study to a variety of α,*β*-unsaturated ketones **1b**−**l**. We decided to use as a catalyst the combination Amberlite IRA900F/TMSN$_3$ which produces in situ the effective Amberlite IRA900N$_3$.

In the presence of 0.1−0.5 molar equiv of Amberlite IRA900F and 1.1−3.0 mol equiv of $TMSN_3$, the azidation of α,*β*-enones proceeded under mild conditions (30 °C or 60 °C) in acceptable reaction times (2.5−24 h).

Cyclic and acyclic enones were converted to the corresponding *β*-azido ketones in satisfactory yields (70−95%). The only exception was benzylidene acetone (**1h**) which gave an unsatisfactory conversion to **2h** (Table 2, entry 8). Aa a result, 36% of **1h** was recovered after silica gel column chromatography, achieving a 70% effective yield.

The reactions of **1e**,**f** were not diasteroselective producing **2e**,**f** in a 60/40 mixture of diastereoisomers (Table 2, entries 5 and 6). The azidations of **1d**,**e** were completely regioselective (Table 2, entries 4 and 5).

All the *β*-azido ketones **2** have been isolated in high purity (>98%) simply by filtration, except in the cases of **2c**,**h**,**i**,**k** (Table 2, entries 3, 8, 9, and 11) that were isolated after silica gel column chromatography. In all the cases, the catalysts have been recovered and re-used for at least five consecutive cycles without the notice of any decrease of their efficiency.

In conclusion, Amberlite IRA900N$_3$ has proved to be an effective anionic catalyst for the activation of the Si−N bond, and the use of SolFC is essential for achieving its maximum efficiency. In addition, our protocol for the preparation of

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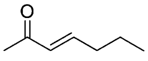
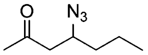
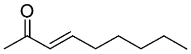
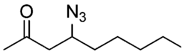
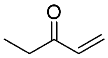
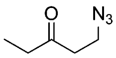
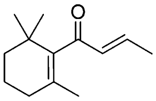
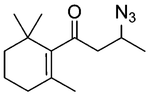
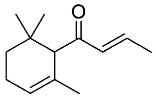
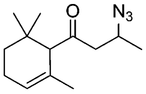
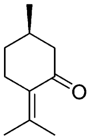
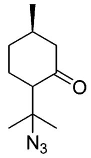
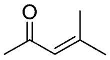
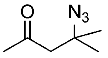
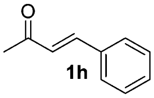
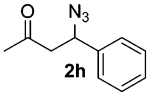
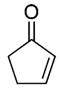
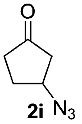
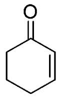
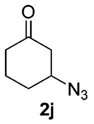
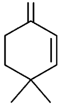
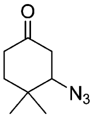
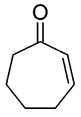
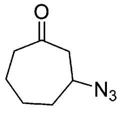
[9] This product was purchased from Aldrich and is produced by Rohm and Haas, and its brand name is "Amberlite IRA900F$^-$ form" or "Fluoride on Amberlyst A-26".

[10] The main difference between the two resins is that Amberlite IRA 400 is a gel-type polystyrene resin with a particle mean size of 0.50−0.75 mm and that Amberlite IRA 900 is a macroreticular polystyrene resin with a particle mean size of 0.65−0.82 mm. Data from Rohm and Haas at http://www.rohmhaas.com.

TABLE 2. Azidation of 1a−l by Using the Amberlite IRA900F/$TMSN_3$ System under SolFC

Entry	Enone	Amberlite IRA900F (molar equiv)	$TMSN_3$ (molar equiv)	T (°C)	t (h)	Adduct	Yield (%)[a]
1	 **1a**	0.10	1.1	60	2.5	 **2a**	90
2	 **1b**	0.10	1.1	60	6	 **2b**	95
3	 **1c**	0.1	1.1	30	5	 **2c**	90
4	 **1d**	0.50	3.0	60	18	 **2d**	95
5	 **1e**	0.25	1.5	60	6	 **2e**	95[b]
6	 **1f**	0.50	1.5	60	24	 **2f**	92[b]
7	 **1g**	0.25	1.5	60	3	 **2g**	82
8	 **1h**	0.50	2.0	60	15	 **2h**	70[c]
9	 **1i**	0.25	3.0	30	4	 **2i**	70
10	 **1j**	0.25	1.5	30	6	 **2j**	95
11	 **1k**	0.25	3.0	60	24	 **2k**	75
12	 **1l**	0.50	3.0	60	18	 **2l**	85

[a] Yield of isolated pure product. [b] 60/40 mixture of diastereoisomers. [c] Effective yield calculated considering that 36% of **1h** was recovered after silica gel column chromatography.

β-azido carbonyls eliminates the use of the organic reaction medium, avoids the use of metallic species, and allows the recovery and re-use of the catalyst, opening an environmentally benign access route to this important class of molecules.

Experimental Section

Representative Experimental Procedure for the Azidation of α,β-Unsaturated Ketones. In a screw capped vial equipped with a magnetic stirrer, (3*E*)-hept-3-en-2-one (**1a**; 0.116 g, 1.0 mmol), Amberlite IRA900F (0.038 g, 0.10 mmol, 2.6 mmol/g), and $TMSN_3$ (0.152 mL, 1.1 mmol) were consecutively added, and the resulting heterogeneous mixture was left under vigorous stirring at 60 °C. After 2.5 h, ethyl acetate was added, the catalyst was recovered by filtration, and the organic solvent was evaporated under vacuum to give $\geq$98% pure 4-azidoheptan-2-one (**2a**) as an oil (90% yield, 0.140 g).

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Supporting Information Available: General experimental procedures and characterization data (^1H NMR, ^{13}C NMR, IR, R_f, mp, and GC-MS analyses) for all compounds and copies of ^1H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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