Poly(ethylene glycol) Grafted onto Dowex Resin: An Efficient, Recyclable, and Mild Polymer-Supported Phase Transfer Catalyst for the Regioselective Azidolysis of Epoxides in Water

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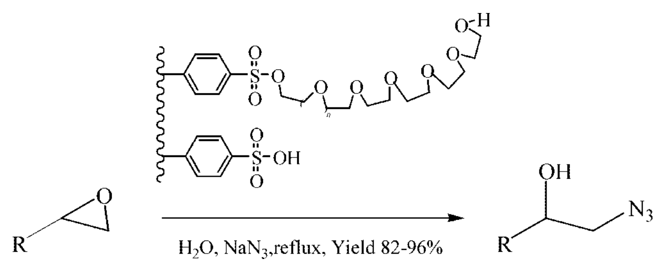

In this study, an efficient method was designed to graft poly(ethylene glycol) effectively onto commercial Dowex resin. The catalytic efficiency of the copolymer obtained as a new solid−liquid phase transfer catalyst was studied. It was proved that this organocatalyst is an efficient heterogeneous catalyst for regioselective azidolysis of epoxide in water and gave azidohydrin in excellent yield under mild reaction conditions. The polymeric catalyst was easily recovered by simple filtration and showed no appreciable loss of activity when recycled several times.

Introduction

Phase transfer catalysis (PTC) is a fascinating area of current research interest, especially for synthetic organic chemists.[1] One practical limitation of the phase transfer method, however, is that many of the catalysts used promote the formation of stable emulsions. Immobilization of the phase transfer catalyst on an insoluble polymeric matrix can provide a simple solution to this problem.[2] This technique would have considerable advantages. Not only would the catalyst recovery and product isolation be greatly simplified but also, owing to the three-phase nature of the system, continuous flow methods could be employed, making the technique particularly attractive for industrial applications.[3] Hence, graft copolymers have been extensively studied recently because of their varied applications.[4]

Poly(ethylene glycol) (PEG) and its derivatives are interesting catalysts[5] and solvents.[6] PEGs are known to be inexpensive and thermally stable, have almost negligible vapor pressure, and are toxicologically innocuous and environmentally benign media for chemical reactions.[7]

By considering the significance of all of the earlier studies in general and the development of water as an eco-friendly medium for organic reactions in particular,[8] we decided to synthesize a novel insoluble polymer-supported phase transfer catalyst by simple grafting of PEG onto Dowex resin to form a unique PTC complex of Dowex−PEG and thus develop an alternative catalytic system for some transformations such as azidolysis of epoxide.

The regioselective formation of β-azido alcohols from azidolysis of epoxides is an important reaction in medicinal and organic chemistry as these are useful synthetic intermediates

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(1) (a) Kawamura, M.; Sato, K. *Chem. Commun.* **2006**, 4718–4719. (b) Shi, Q.; Lee, Y. J.; Kim, M. J.; Park, M. K.; Lee, K.; Song, H.; Cheng, M.; Jeong, B. S.; Park, H. G.; Jew, S. S. *Tetrahedron Lett.* **2008**, *49*, 1380–1383. (c) Kitamura, M.; Arimura, Y.; Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* **2008**, *49*, 2026–2030, and references therein.

(2) (a) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Org. Lett.* **2000**, *2*, 1737–1739. (b) Mahdavi, H.; Tamami, B. *React. Funct. Polym.* **2005**, *64*, 179–185.

(3) Chen, J.; Yang, G.; Zhang, H.; Chen, Z. *React. Funct. Polym.* **2006**, *66*, 1434–1451.

(4) Turi, E. A., Ed. *Thermal Characterization of Polymer Materials*, 2nd ed.; Academic Press: San Diego, CA, 1997.

(5) (a) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. *J. Org. Chem* **2001**, *66*, 3160–3166. (b) Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *J. Mol. Catal. A: Chem.* **2006**, *263*, 186–194.

(6) (a) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64–82. (b) Jorapur, Y. R.; Rajagopal, G.; Saikia, P. J.; Pal, R. R. *Tetrahedron Lett.* **2008**, *49*, 1495–1497.

(7) Du, Y.; Wang, J. Q.; Chen, J. Y.; Cai, F.; Tian, J. S.; Konga, D. L.; Hea, L. N. *Tetrahedron Lett.* **2006**, *47*, 1271–1275, and references therein.

(8) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem.* **2005**, *117*, 3339–3343.

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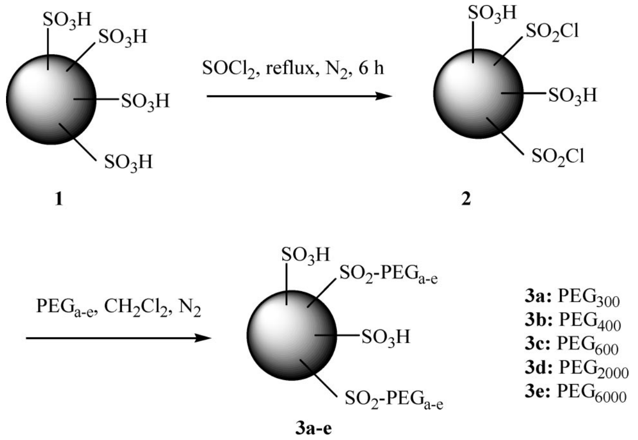
SCHEME 1. Preparation of Dowex-PEGs



for the preparation of β-amino alcohols, vicinal diamines, natural products, and chiral auxiliaries.[9] Generally, azidohydrins are prepared through the ring opening of epoxides using different azides in suitable solvents.[10] Even though the classic protocol[11] uses sodium azide and ammonium chloride, the azidolysis reaction requires a long reaction time (12−48 h) and the azidohydrin is often accompanied by isomerization, epimerization, and rearrangement of products.[12] Although a few reagents and catalysts have been reported recently for the conversion of epoxides to β-azido alcohols,[10,13] disadvantages such as long reaction times, low yields of products, difficulty in preparation and/or storage of reagents or catalysts, tedious workup, and, in most cases, low regioselectivity, clearly identify a need to introduce new methods for such functional group transformations.

Results and Discussion

A series of PEGs with molecular weights of 300, 400, 600, 2000, and 6000 Da can be easily grafted to Dowex Maraton C resin (cat **3a**−**3e**) in the reaction presented in Scheme 1. In the first step, sulfonic acid functional groups of resin were converted to sulfonyl chloride. PEG can be efficiently immobilized on the resin by reaction of sulfonyl chloride functional groups with PEG. The reaction is very clean and does not require any workup procedure because the evolved HCl gas can be removed from the reaction vessel immediately.

To determine the amount of PEG supported on the resin, the degree of immobilization, 0.5 g of the Dowex−SO_3H and Dowex−PEG were washed with methanol, dried, and mixed with 20 mL of 0.5 M NaOH for 1 h. Then, the solutions were titrated with 0.5 M HCl. The degree of immobilization of PEG with different molecular weights is shown in Table 1 and clearly indicates that Dowex−PEG_{300} showed the highest degree of immobilization of PEG units on the main backbone of the resin.

TABLE 1. Amount of PEGs with Different Molecular Weights Supported on Dowex

grafted resins	degree of immobilization
Dowex−PEG_{300}	1.45
Dowex−PEG_{400}	0.95
Dowex−PEG_{600}	0.50
Dowex−PEG_{2000}	0.10<
Dowex−PEG_{6000}	

TABLE 2. Comparison of Various Solvents in Azidolysis of 2,3-Epoxypropyl Phenyl Ether

entry	catalyst	solvent	time (h)	result
1	Dowex−PEG_{300}	CH_2Cl_2	2.0	5% yield
2	Dowex−PEG_{300}	CH_3CN	2.0	7% yield
3	Dowex−PEG_{300}	THF	2.0	5% yield
4	Dowex−PEG_{300}	H_2O	0.75	completed
5	PEG_{300}	H_2O	2.0	some diol was isolated
6	Dowex	H_2O	2.0	some diol was isolated

TABLE 3. Investigation of Catalyst Evaluation of Grafted Polymer

grafted resins	time (min)[a]
Dowex−PEG_{300}	45
Dowex−PEG_{400}	75
Dowex−PEG_{600}	180
Dowex−PEG_{2000}	b
Dowex−PEG_{6000}	

[a] All reaction were carried out under similar conditions. [b] No reaction.

Initially, the ring opening of 2,3-epoxypropyl phenyl ether (1 mmol) with azide anion (1.2 mmol) in the presence of Dowex−PEG_{300} was chosen as a model, and the role of various solvents on the reaction system was investigated. TLC analysis of the reaction mixture did not show completion of the reaction in dichloromethane, chloroform, tetrahydrofuran, and acetonitrile under reflux conditions after 2 h, but surprisingly, in water, the reaction was completed within 45 min (Table 2). The reaction produced 1-azido-3-phenoxypropan-2-ol in quantitative yield. This reaction was also tested, using PEG and Dowex separately; the reaction failed to give the expected product, but after a prolonged reaction time, some diol was isolated.

For the sake of comparison and evaluation, we performed azidolysis of 2,3-epoxypropyl phenyl ether (1 mmol) using the grafted polymers as acidic phase transfer catalysts and sodium azide (1.2 mmol) in water under reflux conditions. Among the five kinds of polymer-supported phase transfer catalysts (**3a**−**3e**, Scheme 1), it was found that Dowex−PEG_{300} had the highest catalytic activity of the grafted polymers (Table 3). We reasoned that this was because of the greater number of PEG units linked to the main backbone of the resin.

In Figure 1, the chemical structure and morphology of the Dowex−PEG_{300} resin are shown by scanning electron microscopy (SEM). According to the obtained results, we tried to use Dowex−PEG_{300} as an efficient and recoverable promoter of ring opening of different types of epoxides by the azide ion in H_2O. To determine the optimum conditions, the conversion of 2,3-epoxypropyl phenyl ether to the corresponding azidohydrine was investigated in the presence of polymeric catalyst as phase transfer catalyst in water. The optimum molar ratio of catalyst

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[9] (a) Horton, D.; Wander, J. D. In *The Carbohydrates*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1980; Vol. 1B, p 643. (b) Schubert, J.; Schwesinger, R.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 167. (c) Lakshman, M.; Nadkarni, D. V.; Lehr, R. E. *J. Org. Chem.* **1990**, *55*, 4892–4897. (d) Serrano, P.; Llebaria, A.; Delgado, A. *J. Org. Chem.* **2002**, *67*, 7165–7167.

[10] Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343–345.

[11] (a) *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

[12] Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **1999**, *64*, 6094–6096, and references therein.

[13] (a) Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* **2001**, *42*, 8721–8724. (b) Spelberg, J. H. L.; Vlieg, J. E. T. H.; Tang, L.; Janssen, D. B.; Kellogg, R. M. *Org. Lett.* **2001**, *3*, 41–43. (c) Sabitha, G.; Babu, R. S.; Reddy, M. S. K.; Yadav, J. S. *Synthesis* **2002**, *15*, 2254–2258. (d) Kazemi, F.; Kiasat, A. R.; Ebrahimi, S. *Synth. Commun.* **2003**, *33*, 999–1004. (e) Iranpoor, N.; Firouzabadi, H.; Shekarize, M. *Org. Biolmol. Chem.* **2003**, *1*, 724–727. (f) Chen, S. W.; Thakur, S. S.; Li, W.; Shin, C. K.; Kawthekar, R. B.; Kim, G. J. *J. Mol. Catal. A: Chem.* **2006**, *259*, 116. (g) Yadollahi, B.; Danafar, H. *Catal. Lett.* **2007**, *113*, 120–123.

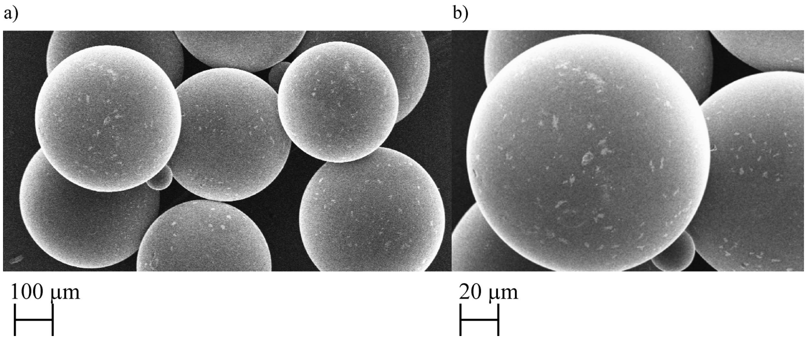
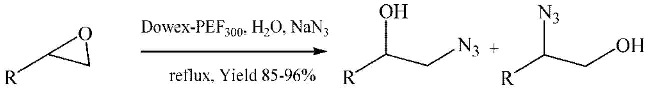
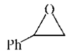
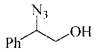
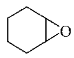
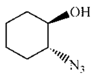
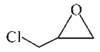
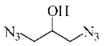
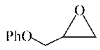
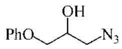
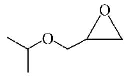
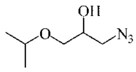
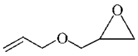
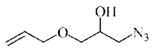
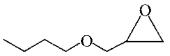
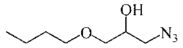
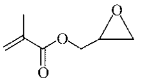
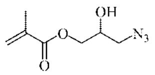
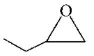
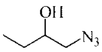
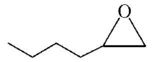
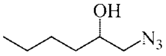
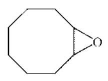
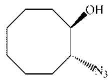


FIGURE 1. SEM micrograph and chemical structure of Dowex−PEG$_{300}$: (a) scale bar = 100 μm, and (b) scale bar = 20 μm.

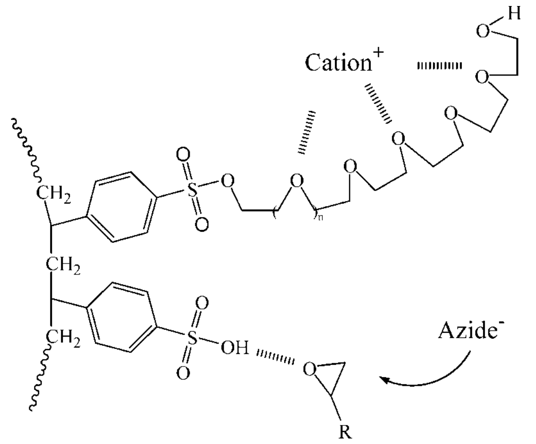
TABLE 4. Dowex−PEG$_{300}$ Catalyzed Regioselective Ring Opening of Epoxides



Entry	Epoxide	Product(s)[a]	Time (h)	Yield (%)[b]
1			0.50	85(10)[c]
2			1.5	85
3			1.25	85[d]
4			0.75	96
5			1.25	90
6			0.45	90
7			1.5	85
8			1.5	90
9			1.5	92
10			1.5	90
11			3.5	8[e]

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples. [b] Isolated yields. [c] According to GC analysis. [d] The molar ratio of epoxide to NaN$_3$ was 1:2.5. [e] Some diol was isolated.

SCHEME 2. Postulated Roles of Dowex−PEG in the Azidolysis of Epoxides



to epoxide was found to be 0.1 g/1 mmol of epoxide. It is also worth mentioning that Dowex−PEG$_{300}$ does not suffer from extensive mechanical degradation after operating at the high stirring rates required by PTC conditions.

The success of this first set of experiments using Dowex−PEG$_{300}$ as a catalyst encouraged us to increase the scope of the reaction to other epoxides (Table 4). Excellent yields of the desired β-azido alcohols were obtained with a reversal of regioselectivity indicating attack at the less substituted carbon of the aliphatic epoxides, while styrene oxide as an aryl epoxide formed the product by attack at the benzylic position. In all cases, a very clean reaction was observed and careful examination of the ^{1}H NMR spectra of the crude products clearly indicated the formation of only one regioisomer in each case (except in entry 1). The probable reason may be that, in styrene oxide, the positive charge on the oxygen appears to be localized on the more highly substituted benzylic carbon leading to the major product,[14] whereas in the case of aliphatic epoxides, steric factors predominate over electronic factors, thereby facilitating attack at the less hindered carbon atom of the epoxide ring. Also, in the case of cyclohexene oxide, the reaction was completely antistereoselective, and the trans product was obtained (Table 4, entry 2). In the case of epichlorohydrin, the diazido alcohol was produced (Table 4, entry 3). The structures of all of the products were determined from their analytical and spectral (IR, ^{1}H NMR) data and by direct comparison with authentic samples.

In the present conversion, the role of Dowex−PEG$_{300}$ is possibly to form complexes with cations, much like crown ethers, and these complexes cause the anion to be activated. In addition, polymeric catalyst can probably facilitate the ring opening of the epoxide by hydrogen bonding as shown in Scheme 2.

While developing a new method for ring opening of epoxide using PTC,[15] we recently reported PEG−SO$_3$H as an acidic phase transfer catalyst.[16] Unfortunately, the use of recycled PEG−SO$_3$H shows a loss in its activity reflected in the yield of

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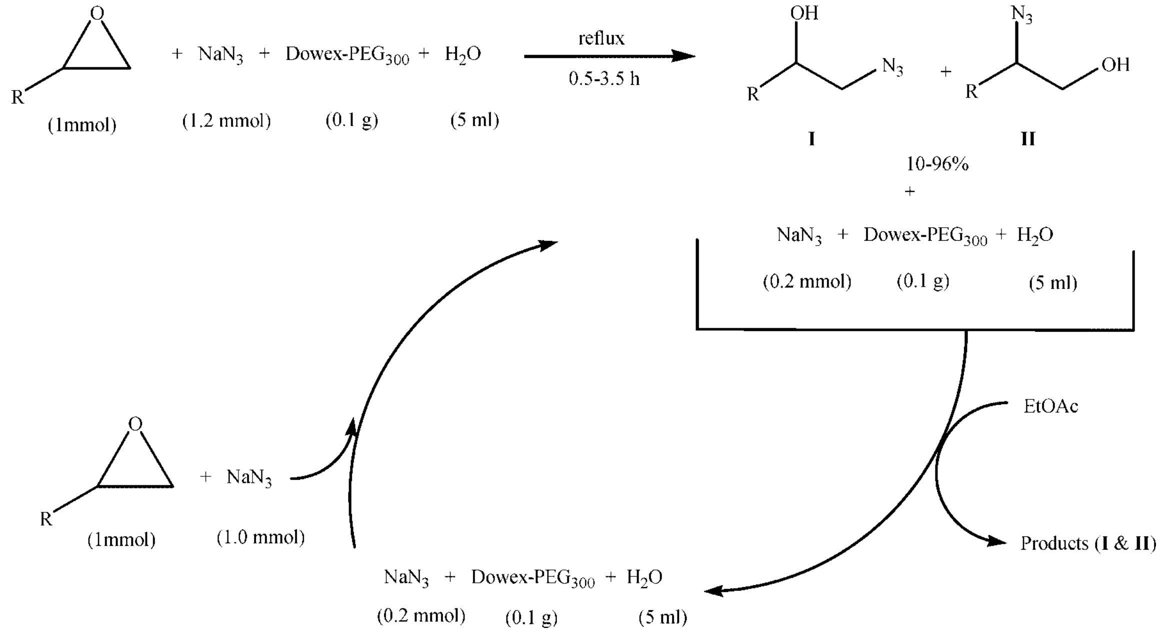
(14) Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1998**, *39*, 7971–7974.

(15) (a) Li, J. T.; Liu, X. F. *Ultrason. Sonochem.* **2008**, *15*, 330–333. (b) Kiasat, A. R.; Zayadi, M. *Catal. Commun.* **2008**, *9*, 2063–2067.

SCHEME 3. Facile Nucleophilic Ring Opening of Epoxides in the Atom Economical Method



ring opening of epoxide. The most ideal synthetic methodology could be defined as a system wherein 100% atom economy is preserved, the solvent is recycled to the fullest extent, and the catalyst or excess of reagent remains throughout in the solvent medium and without losing activity for several runs. In general, the methodology worked well independently on the nature of the epoxide, furnishing the corresponding azido alcohols in high yields. The Dowex−PEG$_{300}$ and the additional sodium azide (0.2 mmol) were conveniently separated from the reaction mixture by simple extraction of product in ethyl acetate phase. The aqueous phase was reused three consecutive times with only a slight variation in the yields of the corresponding products. Scheme 3 describes the facile nucleophilic ring opening of epoxides with sodium azide in the atom economical method.

To evaluate the efficiency of this method for the scaling up experiment, transformation of 2,3-epoxypropyl phenyl ether and cyclohexene oxide was also performed on a 100 mmol scale. Gratifyingly, both substrates provided the corresponding azido alcohol without appreciable decrease in the yields.

In conclusion, we have reported the first example of the use of PEG supported on Dowex resin as an efficient and reusable heterogeneous catalyst in the regioselective azidolysis of epoxides in water. The reactions generated the corresponding products with satisfactory yields. Moreover, the catalytic material is easily recovered and can be recycled at least three times without loss of activity. These results broaden the scope of this organocatalyst as a new solid−liquid phase transfer catalyst.

Experimental Section

Typical Procedure for Grafting of the Poly(ethylene glycol) to Dowex Maraton C. Two grams of Dowex H$^+$ resin (Mesh 30−40) was washed with cold methanol and dried under vacuum at 50 °C. Then the polymer was refluxed with freshly distilled $SOCl_2$ (5.0 mL, 67 mmol). After stirring for 6 h, the excess unreacted thionyl chloride was distilled out. To the resulting polymer was added a solution of PEG (5.0 mL, $M_w = 300$) in dried dichloromethane (5.0 mL), and the solution was mixed at room temperature until no HCl was produced. The solid was filtered off and washed thoroughly with acetone. Then the Dowex−PEG$_{300}$ was collected and dried in vacuum.

Typical Procedure for the Regioselective Ring Opening of Epoxides. To a mixture of epoxide (1.0 mmol) and Dowex−PEG$_{300}$ (0.1 g) in water (5.0 mL) was added NaN_3 (1.2 mmol). The suspension was magnetically stirred under reflux conditions for the time shown in Table 4. After complete consumption of epoxide as judged by TLC (using *n*-hexane/ethylacetate (5:1) as eluent), the insoluble PTC was filtered off and the filtrate was extracted with EtOAc (3 × 5). The extract was washed with water, dried over Na_2SO_4, and evaporated in vacuo to give the azidohydrines in 85−96% isolated yields. For styrene oxide, further purification was achieved by preparative TLC or by silica gel column chromatography.

2-Azido-2-phenyl-1-ethanol: IR (neat) ν N_3 (2102 cm^{-1}); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (br s, 1H), 3.73 (d, 2H), 4.65 (t, 1H), 7.20−7.40 (m, 5H).

2-Azidocyclohexan-1-ol: IR (neat) ν N_3 (2097 cm^{-1}); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.36 (m, 4H), 1.72−1.78 (m, 2H), 2.00−2.07 (m, 2H), 2.52 (s, 1H), 3.10−3.22 (m, 1H), 3.28−3.42 (m, 1H).

Acknowledgment. We are grateful to the Research Council of Chamran University for financial support.

Supporting Information Available: Experimental procedures and characterization of some products in Table 4 and SEM figures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801356Y

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(16) Kiasat, A. R.; Fallah Mehrjardi, M. *Catal. Commun.* **2008**, *9*, 1497–1500.