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SHORT COMMUNICATIONS

Dedicated to Professor Miguel Yus on the 60th anniversary of his birth

Poly(*N*-vinylimidazole) as Efficient and Recyclable Catalyst for the Addition of Thiols to Michael Acceptors in Aqueous Medium

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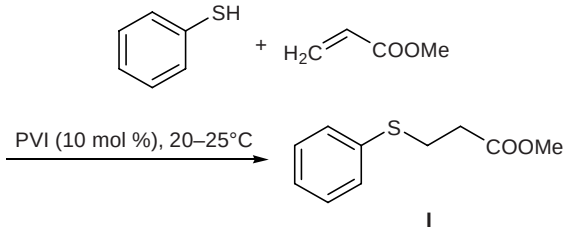
Imidazole ring is a structural fragment of the amino acid histidine which is included in almost all enzymes. It is known that imidazole is capable of catalyzing a number of biochemical processes [1, 2]. We previously showed that poly(*N*-vinylimidazole) can be used as polymeric support (ligand) for palladium and that such system is an efficient and recyclable catalyst for cross-coupling reactions [3]. Moreover, poly(*N*-vinylimidazole) successfully simulates natural enzymes based on peptide macromolecules [4].

Taking into account the ability of imidazole to catalyze certain reactions, we though it to be expedient to test it for catalytic activity in analogous processes. Potential advantages of poly(*N*-vinylimidazole) as catalyst are its solubility in water and aqueous media and the possibility for repeated use.

Conjugate addition of thiols to α,β-unsaturated carbonyl compounds underlies a widely used method for the synthesis of β-sulfanyl-substituted carbonyl derivatives which exhibit biological activity [5]. Search for simple and efficient procedures for the preparation of such compounds was especially intense in the past decade and is now in progress [6–17]. Here, specific attention is given to the use of nontoxic solvents and catalysts [10–17].

Scheme 1.



I

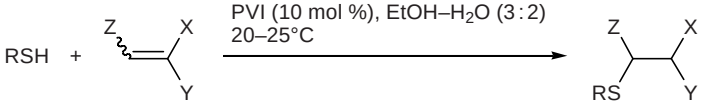
In the present study we made an attempt to catalyze addition of thiols to Michael acceptors in aqueous or aqueous–alcoholic medium at room temperature by poly(*N*-vinylimidazole) with a molecular weight of 75300 as recyclable organic catalyst. It is known that benzenethiol adds at the double C=C bond in electron-deficient olefins in the absence of a catalyst [12].

Table 1. Reaction of benzenethiol with methyl acrylate[a]

Run no.	Solvent	Reaction time, h	Yield,[b] %
1	No solvent	24	50
2	EtOH	4	19
		24	58
3	H_2O	4	95 (10)
4	EtOH–H_2O, 1:1[c]	4	98
5	EtOH–H_2O, 3:2[d]	4	100 (33)
6	*i*-PrOH–H_2O, 1:1[d]	4	72

[a] Molar ratio thiol–alkene–PVI (monomer unit) 1.0:1.2:0.1.
[b] According to the ^{1}H NMR data using dimethyl terephthalate as reference. In parentheses is given the yield in the absence of catalyst.
[c] Heterogeneous mixture.
[d] Homogeneous mixture.

Scheme 2.



I–XII

I–VI, R = Ph; **VII–XII**, R = *n*-C_6H_{13}; **I**, **VII**, X = COOMe, Y = Z = H; **II**, **VIII**, X = CN, Y = Z = H; **III**, **IX**, X = Z = COOMe, Y = H; **IV**, **X**, X = COOEt, Y = Me, Z = H; **V**, **XI**, X = COOMe, Y = CH_2COOMe, Z = H; **VI**, **XII**, XZ = $C(O)CH_2CH_2CH_2$, Y = H.

However, reactions of alkanethiols with unsaturated compounds used in the present work required the presence of a base.

Using the reaction of benzenethiol with methyl acrylate as model (Scheme 1) we found optimal conditions for the process: solvent ethanol–water (3:2), reaction time 4 h (Table 1), amount of poly(*N*-vinylimidazole) (PVI) 10 mol %. Obviously, the presence of water is important. It favors dissociation of benzenethiol, while PVI (being a base) acts as proton carrier. The reaction occurs under mild conditions (room temperature), and the yield of methyl 3-(phenylsulfanyl)propionate is quantitative. Using the same model reaction (Table 1, run no. 5) we examined the possibility for recycling of the catalyst. In each subsequent cycle, after removal of compound **I** from the reaction mixture by extraction, required amounts of water, ethanol, and reactants were added to the remaining aqueous phase. We observed no loss in catalytic activity in five consecutive cycles: the yields of methyl 3-(phenylsulfanyl)propionate (**I**) were 100, 99, 100, 100, and 100%, respectively (according to the ^{1}H NMR data).

Likewise, Michael addition of benzenethiol to other electron-deficient olefins smoothly occurred under the above conditions (Scheme 2, Table 2). Exceptions were only olefins having a substituent in the α-position with respect to the electron-withdrawing group. Presumably, the reason is reduced electrophilicity of the double bond due to the presence of a donor group rather than steric factor (cf. run nos. 4, 5 and 10, 11; Table 2). Not only benzenethiol but also hexane-1-thiol reacted with the olefins used. However, the most important is that the catalyst can be readily separated from the product and used repeatedly.

Thus we showed that poly(N-vinylimidazole) is an accessible, effective, and recyclable organic catalyst for the addition of aromatic and aliphatic thiols to Michael acceptors; it ensures the reaction to be performed in nontoxic aqueous or aqueous–alcoholic medium under mild conditions. Studies aimed at ex-

Table 2. Addition of thiols to activated alkenes in ethanol–water (3:2) at 20–25°C[a]

Run no.	Thiol	Alkene	Reaction time, h	Product	Yield,[b] %
1	PhSH	CH_2=CHCOOMe	4	**I**	99
2	PhSH	CH_2=CHCN	5	**II**	95
3	PhSH	MeOC(O)CH=CHCOOMe-*trans*	3	**III**	92
4	PhSH	CH_2=C(Me)COOEt	6 (50°C) + 6 (80°C)	**IV**	20[c]
5	PhSH	MeOC(O)C(=CH_2)CH_2COOMe	48	**V**	82
6	PhSH	Cyclohex-2-en-1-one	3	**VI**	99
7	*n*-C_6H_{13}SH	CH_2=CHCOOMe	2	**VII**	95
8	*n*-C_6H_{13}SH	CH_2=CHCN	2	**VIII**	87[c]
9	*n*-C_6H_{13}SH	MeOC(O)CH=CHCOOMe-*trans*	2	**IX**	97[c]
10	*n*-C_6H_{13}SH	CH_2=C(Me)COOEt	48	**X**	11[c]
11	*n*-C_6H_{13}SH	MeOC(O)C(=CH_2)CH_2COOMe	48	**XI**	93[c]
12	*n*-C_6H_{13}SH	Cyclohex-2-en-1-one	3	**XII**	93

[a] Molar ratio thiol–alkene–PVI (monomer unit) 1.0:1.2:0.1.
[b] Yield of the isolated product.
[c] According to the ^{1}H NMR data using dimethyl terephthalate as reference.

tending the scope of application of this catalyst with respect to other substrates are now in progress.

Poly(*N*-vinylimidazole), *M* 75300, was synthesized according to the procedure described in [3].

Addition of thiols to electron-deficient alkenes in the presence of poly(*N*-vinylimidazole (*general procedure***).** Poly(*N*-vinylimidazole), 9.4 mg (0.1 mmol, calculated per monomer unit), was dissolved in 5 ml of a 3:2 ethanol–water mixture, 1.2 mmol of the corresponding alkene and 1 mmol of thiol were added, and the mixture was stirred at room temperature until the reaction was complete (Table 2). The mixture was then extracted with methylene chloride, the extract was dried over sodium sulfate, the solvent was distilled off under reduced pressure, and the product was isolated by column chromatography using methylene chloride–petroleum ether as eluent. Compounds **I**–**XII** were colorless liquids. Their structure was confirmed by the ^{1}H and ^{13}C NMR and MALDI-TOF mass spectra. The spectral data for the newly synthesized compounds are given below.

Dimethyl 2-(phenylsulfanylmethyl)succinate (V). ^{1}H NMR spectrum, δ, ppm: 2.74 d.d (1H, CH_2CO, *J* = 5.3, 16.8 Hz), 2.82 d.d (1H, CH_2CO, *J* = 7.3, 16.8 Hz), 3.04–3.12 m (2H, CH_2S), 3.34 m (1H, CHCO), 3.66 s (6H, CH_3O), 7.23 t (1H, *p*-H, *J* = 7.3 Hz), 7.30 t (2H, *m*-H, *J* = 7.6 Hz), 7.39 d (2H, *o*-H, *J* = 7.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 34.44 (CH_2), 35.40 (CH_2S), 41.13 (CH), 51.81 (CH_3O), 52.11 (CH_3O), 126.73 (C^p), 129.05 (C_{arom}), 130.19 ($_{arom}$), 134.97 (C^i), 171.88 (CO), 173.33 (CO). Mass spectrum: *m*/*z* 268 (100%) $[M]^+$.

3-(Hexylsulfanyl)propionitrile (VIII). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, *J* = 6.8 Hz), 1.23–1.32 m [4H, $CH_3(CH_2)_2$], 1.33–1.42 m [2H, $CH_3(CH_2)_2CH_2$, *J* = 7.0 Hz], 1.53–1.62 m [2H, $CH_3(CH_2)_3CH_2$, *J* = 7.4 Hz], 2.58 t (2H, CH_2S, *J* = 7.4 Hz), 2.62 t (2H, SCH_2CH_2CN, *J* 7.3 Hz), 2.77 t (2H, SCH_2CH_2CN, *J* = 7.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.89 ($C^{6'}$), 18.83 (C^2), 22.42 ($C^{5'}$), 27.56 (C^3), 28.34 ($C^{3'}$), 29.33 ($C^{2'}$), 31.27 ($C^{1'}$ or $C^{4'}$), 32.24 ($C^{1'}$ or $C^{4'}$), 118.30 (CN). Mass spectrum: *m*/*z* 171 (100%) $[M]^+$.

Dimethyl 2-(hexylsulfanyl)succinate (IX). ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3, *J* = 7.0 Hz), 1.21–1.29 m [4H, $CH_3(CH_2)_2$], 1.30–1.37 m [2H, $CH_3(CH_2)_2CH_2$], 1.49–1.61 m [2H, $CH_3(CH_2)_3CH_2$, *J* = 7.1 Hz], 2.56–2.69 m (3H), 2.98 d.d (1H, *J* = 9.8, 16.9 Hz), 3.64 d.d (1H, *J* = 5.6, 9.8 Hz), 3.66 s (3H, CH_3O), 3.73 s (3H, CH_3O). ^{13}C NMR spectrum, δ_C, ppm: 13.88 ($C^{6'}$), 22.39 ($C^{5'}$), 28.34 ($C^{3'}$), 29.03 ($C^{2'}$), 31.23 ($C^{1'}$ or $C^{4'}$), 31.43 ($C^{1'}$ or $C^{4'}$), 36.26, 41.31, 51.88 (CH_3O), 52.19 (CH_3O), 171.08 (CO), 172.18 (CO). Mass spectrum: *m*/*z* 262 (100%) $[M]^+$.

Ethyl 3-(hexylsulfanyl)-2-methylpropionate (X). ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3, *J* = 6.8 Hz), 1.23–1.43 m [12H, CH_3, $CH_3(CH_2)_3$], 1.55–1.60 m [2H, $CH_3(CH_2)_3CH_2$], 2.52 t (2H, CH_2S, *J* = 7.4 Hz), 2.56 d.d (1H, CH_2CH, *J* = 6.9, 12.8 Hz), 2.62–2.71 m (1H, CHMe), 2.84 d.d (1H, CH_2CH, *J* = 6.9, 12.8 Hz), 4.16 q (2H, CH_2O, *J* = 7.1 Hz). Mass spectrum: *m*/*z* 232 (100%) $[M]^+$.

Dimethyl 2-(hexylsulfanylmethyl)succinate (XI). ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, CH_3, *J* = 6.8 Hz), 1.20–1.29 m [4H, $CH_3(CH_2)_2$], 1.29–1.38 m [2H, $CH_3(CH_2)_2CH_2$], 1.48–1.58 m (2H, *J* = 7.3 Hz), 2.47 t (2H, *J* = 7.3 Hz), 2.63 d.d (1H, *J* = 8.1, 13.4 Hz), 2.68 d.d (1H, *J* = 5.6, 17.1 Hz), 2.75 d.d (1H, *J* = 8.1, 16.9 Hz), 2.85 d.d (1H, *J* = 5.9, 13.5 Hz), 3.03 m (1H), 3.65 s (3H, CH_3O), 3.69 s (3H, CH_3O). ^{13}C NMR spectrum, δ_C, ppm: 13.88 ($C^{6'}$), 22.41 ($C^{5'}$), 28.34 ($C^{3'}$), 29.28 ($C^{2'}$), 31.26 ($C^{1'}$ or $C^{4'}$), 32.36 ($C^{1'}$ or $C^{4'}$), 33.36 (CH_2), 34.59 (CH_2S), 41.34 (CH), 51.71 (CH_3O), 51.99 (CH_3O), 172.04 (CO), 173.67 (CO). Mass spectrum: *m*/*z* 276 (100%) $[M]^+$.

3-(Hexylsulfanyl)cyclohexanone (XII). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, *J* = 6.7 Hz), 1.24–1.32 m (4H), 1.32–1.41 m (2H), 1.52–1.60 m (2H, *J* = 7.5 Hz), 1.66–1.76 m (2H), 2.09–2.18 m (2H), 2.29–2.41 m (3H), 2.54 t (2H, *J* = 7.5 Hz), 2.70 d.d (1H, *J* = 4.3, 14.2 Hz), 3.01–3.09 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 13.97 ($C^{6'}$), 22.48 ($C^{5'}$), 24.25, 28.58, 29.64, 30.53, 31.37, 31.65 (CH_2), 40.93 (C^3), 42.74 (C^6), 48.24 (C^2), 208.97 (CO). Mass spectrum: *m*/*z* 214 (100%) $[M]^+$.

All reactions were carried out under argon. Their progress was monitored by TLC on 60 F_{254} silica gel plates (Merck). Silica gel Merck 60 (0.040–0.063 mm) was used for column chromatography. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer at 400.13 and 100.61 MHz, respectively, using $CDCl_3$ as solvent. MALDI-TOF mass spectra were obtained on a Bruker Daltonics Ultraflex instrument.

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