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Soluble Polymer-Supported Synthesis of Tertiary Amines

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ABSTRACT

The synthesis of tertiary amines on a modified soluble polymer, poly(ethylene glycol) (PEG), is described. The PEG-bound quaternary intermediates were assembled via Michael addition reaction, followed by alkylation. Cleavage from the soluble polymer support was induced by insoluble weak basic resin, to afford the target tertiary amines in excellent purity.

Key Words: Tertiary amine; Soluble polymer; Support; Synthesis.

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It is known that tertiary amines are an extremely important class of compounds from the drug discovery perspective. Indeed more than a quarter of registered drugs are tertiary amines.^[1] Insoluble polymer-supported synthesis of tertiary amines based on the classical Michael addition and Hofmann elimination reactions has been described.^[2] However, the insoluble polymer hampers routine reaction monitoring.

Hofmann elimination reaction itself requires tertiary amine which increases the difficulty of removal of the unwanted triethylamine hydrobromide or iodide salts and needs long reaction time at high temperature in the elimination step.^[3]

Organic synthesis on soluble polymer-supports is currently receiving a great deal of attention^[4,5] and has the potential to combine the best aspects of both solid-phase chemistry and solution-phase chemistry.

As a continuation of our efforts to utilize soluble polymer-supported systems in organic synthesis.^[6] we now first report in this article the synthesis of tertiary amines using PEG as soluble polymer-supports, insoluble weak basic resin I as base and scavengers. The synthetic route is illustrated in Sch. 1, i.e., utilizing PEG derivatized as the acrylate ester II. Michael addition reaction of a secondary amine III to II affords the PEG-bound tertiary amine IV. Quaternization of the tertiary amine IV with an alkyl halide V to give VI introduces another site of diversity and activates the linker for cleavage by a facile Hofmann elimination reaction. During the course of preparing IV and VI, the reaction can take place homogeneously for II and IV which can dissolve in DMF. At the end of reactions, precipitation of IV and VI by adding icy-cold dry Et₂O (10 folds of the solution) to the solution, filtering and washing the PEG-bound product by icy-cold dry Et₂O affords IV and VI. TLC (silica gel, acetone/petroleum ether =1:4 as eluent) showed that the polymer contained no secondary amine or alkyl halide. Afterwards, the tertiary amine VIII was liberated from VI utilizing insoluble weak basic resin I at



Scheme 1.

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room temperature and regenerated II. Filtration of the mixture gave excessive I, VII and a solution of II and VIII in CH_2Cl_2 . Separation of II and VIII can be easily realized by precipitating II using icy-cold Et_2O . Finally, VIII was obtained in 95–98% purity.

It is worth being mentioned that, in each step of the sequence, the PEG-bound products were precipitated selectively and the excess low molecular reagents and the by-products were removed by simple filtration and were easily detected by TLC which was used to confirm the complete removal of the reagent in excess and the soluble by-products, the PEGbound intermediates were easily analyzed to confirm the structure with routine analytical methods (UV, IR, HNMR) without following cleave-&-analyze technique or spectral analyze technique.^[7] During the course of preparing II and VIII, use of I as base and scavengers^[8] largely simplified the purification procedure and facilitated spectral analysis of the PEG-bound products and final products comparing with the reported methods, in which polar trialkylamine hydrochloride or iodide was difficult to be disposed of during reaction work-up. Addition of the mixture of I and VII to 1 M Na₂CO₃ in water regenerated I which can be reused. II recycled in Hofmann elimination reaction can also be reused.

Table 1 shows the representative tertiary amines that have been prepared by this route. The purity of the products is excellent, which may be due to the fact that only the desired PEG-bound quaternized amine **VI** was susceptible to the cleavage conditions by use of the insoluble weak basic resin. The very low yields (21%, 23%) obtained for two of the transformations in Table 1 were thought to be owing to poor quaternization of ethyl bromide.

In conclusion, use of PEG as the soluble polymer support provided a facile method for the synthesis of tertiary amines. Insoluble weak basic resin simplified the purification. Further explorations for extending the application of this method to the synthesis of focused libraries are being developed and will be reported in due course.

EXPERIMENTAL

All organic solvents were dried by standard methods. All PEG samples were melted at 80° C in vacuum for 30 min before use to remove traces of moisture. After reaction, products were purified by evaporation of the reaction solvent in vacuum, followed by addition of the residue dissolved in a few of CH₂Cl₂ to Et₂O, stirred and cooled for 20–30 min

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Table 1. Synthesis of tertiary amines using PEG as soluble polymer-supports.

$R^{1}R^{2}NH$ (III)	$R^{3}X(V)$	Product ^a (VIII)	Yield ^b (purity ^c) (%)
H-NEt ₂	CH ₃ I	R^3 -NEt ₂	65 (97)
	C_2H_5Br		21 (95)
	CH ₂ =CHCH ₂ Br		70 (98)
	\bigcirc -CH ₂ Br		78 (97)
H-N	CH ₃ I	R^3-N	68 (95)
	C_2H_5Br		23 (97)
	CH2=CHCH2Br		74 (95)
	CH ₂ Br		71 (98)

^aThe structure of the obtained tertiary amines was confirmed through the IR and ¹H NMR and also by comparison with authentic samples.

^bCrude overall yield calculated based on the capacity of PEG. ^cDetermined by GC.

at 0°C. The obtained suspension was filtered and the solid was repeatedly washed with cold Et_2O . Melting points were determined on an electrothermal melting point apparatus and were uncorrected. GC was recorded on Shimadzu 16A instrument. IR spectra were recorded using KBr pellets on an IR-Spectrum One (PE). ¹H NMR spectra were recorded on Brucker Ac-80 instrument using CDCl₃ as solvents and TMS as internal standard.

Preparation of PEG-Bound Acrylate (II)

Dry PEG (4.0 g), insoluble weak basic resin I (8.0 g) [Nankai University Chemical Corporation, \geq 4.3 mmol/g], and acryloyl chloride (1.6 mL, 20 mmol) were stirred in DMF (30 mL) for 5 h at 20°C. Then, the mixture was filtered under aspirator pressure using a fritted funnel and washed with DMF (3 × 5mL). The solution was concentrated in vacuum and precipitated by adding icy-cold Et₂O (10 folds of the left solution). The PEG-bound product was then filtered and washed 3 times with Et₂O. The crude PEG-bound product was redissolved, precipitated once and dried in vacuum to give II.

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General Procedure for the Preparation of PEG-Bound Tertiary Amines (IV)

A portion of the PEG-bound product II (2.8 g) was dissolved in a mixture of DMF (15 mL) and amines III (2.0 mL) and agitated for overnight at 20°C. The solution was precipitated by icy-cold Et_2O . The polymer was filtered, redissolved in DMF (4 mL), precipitated once and dried in vacuum to give IV.

General Procedure for the Preparation of PEG-Bound Quaternary Ammonium Salts (VI)

The PEG-bound product IV (1.9 g) was dissolved in a mixture of DMF (15 mL) and alkyl halide (16.0 mmol) and agitated for 15 h at 20°C. The solution was precipitated by icy-cold Et_2O . The polymer was filtered, redissolved with CH_2Cl_2 (4 mL), precipitated once and dried in vacuum to give VI.

General Procedure for the Preparation of Tertiary Amines (VIII)

The PEG-bound product VI (1.7 g) and resin I (1.0 g, 4.3 mmol) were added to CH₂Cl₂ (15 mL) and agitated for 18 h at 20°C. The resin I was filtered and washed with CH₂Cl₂ (3 × 4mL). The filtrate was concentrated and precipitated by addition of icy-cold Et₂O. The PEG product II was then filtered and washed 3 times with Et₂O. The polymer was filtered, redissolved in CH₂Cl₂ (4 mL), precipitated once and dried in vacuum for reuse. The crude PEG-bound product II was also redissolved, precipitated once and dried in vacuum for reuse. The combined filtrate was dried to afford crude product. The purity of this compound was determined to be 98% by GC and could be illustrated by IR and ¹H NMR.

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REFERENCES

- 1. This estimate was obtained by searching the World Drugs Index (Derwent Information Ltd.) for compounds with a tradename containing a tertiary amine group.
- Morphy, J.R.; Rankovic, Z.; Rees, D.C. Tetrahedron Lett. 1996, 37, 3209.
- 3. Cai, J.Q.; Wathey, B. Tetrahedron Lett. 2001, 42, 1383.
- 4. Parrick, H.Y.; Kim, D.J. Acc. Chem. Res. 2000, 33, 546.
- 5. Chen, Z.X.; Zhang, Z.J.; Yang, G.C. Chin. J. Org. Chem. 2001, 21, 263.
- 6. Chen, Z.X.; Yang, G.C.; Zhang, Z.J. Synthesis 2001, 1483.
- Luo, Y.; Ouyang, X.H.; Robert, W.A. Murphy, M.M. J. Org. Chem. 1998, 63, 8719.
- 8. Parlow, J.J. Tetrahedron Lett. 1996, 37, 5257.

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