Poly(ethylene glycol)-Supported 4-Alkylthio-Substituted Aniline − a Useful Starting Material for the Soluble Polymer-Supported Synthesis of Imines and 1,2,3,4-Tetrahydroquinolines

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Keywords: Multicomponent reactions / Polymers / Schiff bases / Synthetic methods

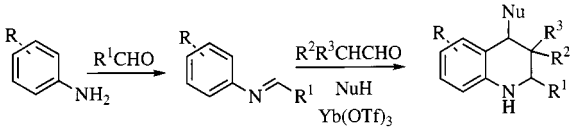
A 4-alkylthio-substituted aniline anchored to a modified poly(ethylene glycol) of M_w = 5000 was selected as a convenient starting material for the liquid-phase synthesis of various imines. Some of these imines were employed in a three-component synthesis of 1,2,3,4-tetrahydroquinolines, carried out in the presence of 2-methylpropanal, different nucleophiles, and catalytic amounts of $Yb(OTf)_3$. Four-component versions of this reaction were also performed. Traceless removal of the heterocycles from the polymer support was accomplished by a reductive desulfurization reaction.

Introduction

Poly(ethylene glycol)s (PEGs) have recently emerged as very convenient supports for the synthesis of a variety of small organic molecules.[1−3] PEGs are inexpensive and commercially available polymers[4] that can readily be functionalized with different spacers and linkers.[5] Provided that their M_w is > 2000 Daltons, PEGs are soluble in many, mostly polar, solvents (including water) and insoluble in a few nonpolar solvents (hexanes, diethyl ether, *tert*-butyl methyl ether).

Because of this solubility profile, PEG supports combine the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena,[6] analytical simplicity) and of solid-phase methods (ready isolation and purification of products).[7−9] As a consequence, syntheses and immobilization of several organic molecules on PEGs have been extensively reported over the last few years.[10−24] In the meantime, solutions have been proposed to circumvent some of the problems associated with the use of PEG supports, such as the low number of functional groups per gram of polymer (loading)[25] and the difficulty of purification of PEG-supported compounds from reagents and by-products with solubility profiles similar to those of the PEGs.[26]

The application of PEG-supported chemistry to the field of combinatorial chemistry is particularly attractive, since the nontoxic and biocompatible nature of this polymeric support should, in principle, allow biological evaluation of the library components to be performed directly on the PEG-anchored molecules.[1−3,27] We have recently reported[28] a new synthesis of 1,2,3,4-tetrahydroquinolines (THQs) from an imine (which can also be generated in situ), an α-branched aldehyde, and a nucleophile, carried out in the presence of catalytic amounts of $Yb(OTf)_3$ (Scheme 1).



R = H, Me, MeO, F, Cl; R^1 = Aryl, Alkyl, heteroAryl, COOEt; R^2, R^3 = Alkyl, OAlkyl; NuH = AlkylOH, ArSH, $ArNH_2$, H_2O.

Scheme 1. Multicomponent synthesis of THQs

The multicomponent nature[29−32] of this process makes it particularly attractive for the preparation of a library of THQs, a class of compounds endowed with a number of interesting biological properties.[33,34] As a prerequisite for this application, we decided to develop the synthesis of a PEG-supported aniline properly functionalized so as to allow firstly the easy formation of *N*-aryl imines, secondly their conversion into differently substituted, supported THQs,[35] and finally the traceless removal of the obtained THQs from the polymer support. We report the results of this study here.

Results and Discussion

On the basis of our experience in the PEG-supported synthesis of imines and β-lactams,[10] mesylate **1**, obtained in three steps and 95% overall yield from the monomethyl ether of PEG with M_w = 5000 (MeOPEG), was selected as

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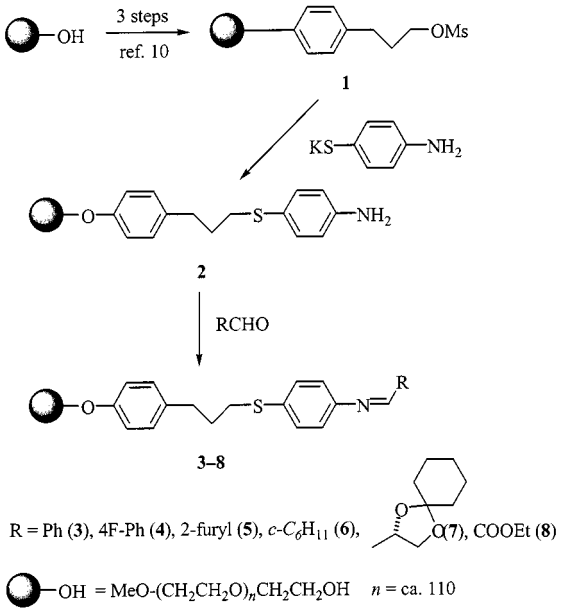
starting material (Scheme 2). Treatment of **1** with the potassium salt of 4-aminothiophenol in DMF gave amine **2** in quantitative yield.



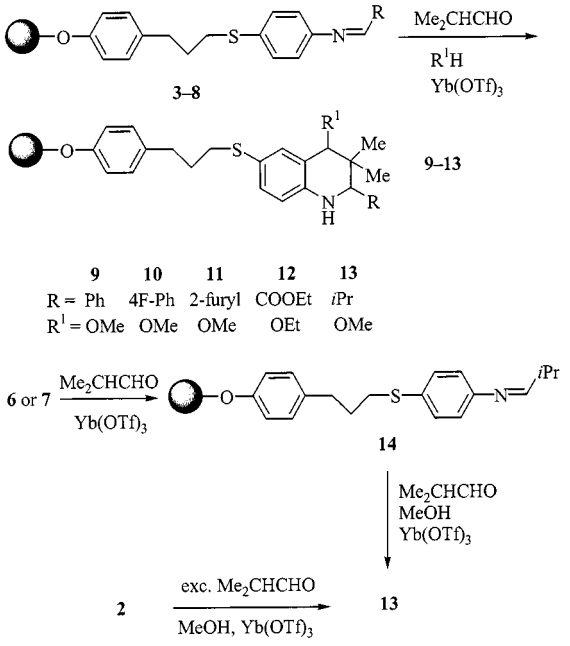
Scheme 2. Synthesis of PEG-supported aniline **2** and imines **3**−**8**

The structure of **2** was designed to feature a spacer (the 4-propylphenoxy group) to separate the reactive functionalities from the PEG core,[36] and a terminal group (the 4-thioaniline moiety) containing part of the THQ skeleton and a handle to allow the traceless removal[37] of the product by reductive desulfurization (the benzeneamino group and the sulfur atom, respectively).

Starting from amine **2**, representative imines **3**−**8**, derived from structurally different aldehydes, were prepared by three methods.[10] Compounds **3**−**5** were synthesized by heating a neat mixture of **2** and the required aldehyde (5 mol-equiv.) at 80−90 °C for 12−24 h. Imines **6** and (*S*)-**7** were obtained by stirring a solution of **2** and the required aldehyde (5 mol-equiv.) in a 30:70 mixture of dichloromethane (DCM) and trimethyl orthoformate for 43 h at room temperature in the presence of 3-Å molecular sieves. Compound **8** was prepared by heating a suspension of **2** and ethyl glyoxylate (50% solution in toluene, 3 mol-equiv.) under reflux in toluene for 24 h.

Imines **3**−**8** were isolated in ≥ 95% yield by precipitation with diethyl ether and filtration. The products were shown to be pure within the detection limits of 300 MHz ^{1}H NMR spectroscopy (see the Exp. Sect. for yield and purity determination of PEG-supported compounds). Since a single H−C=N signal was observed for each imine, the more stable (*E*) configuration was tentatively assigned to these compounds.

The PEG-supported imines thus obtained were then subjected to three-component reactions (96 h at room temp. or 24 h at reflux) with 2-methylpropanal (2 mol-equiv.) and MeOH as both the nucleophile and the reaction solvent, in the presence of 0.3 mol-equiv. of $Yb(OTf)_3$ (Scheme 3). In the case of imine **8**, MeOH was replaced by EtOH to prevent transesterification.[38] Since this imine was not soluble in EtOH, the reaction was carried out in DCM.



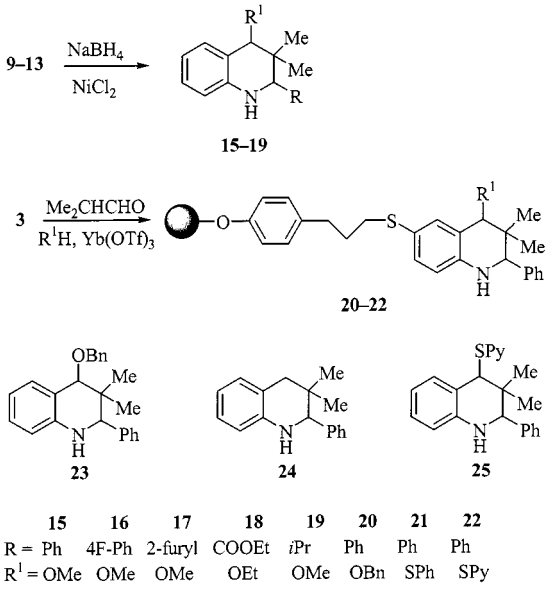
Scheme 3. Synthesis of PEG-supported THQs **9**−**13**

From these reactions, only the THQs **9**−**12** derived from nonenolizable imines **3**−**5** and **8** were isolated by the usual precipitation/filtration procedure. On the other hand, the use of enolizable imines **6** and **7** resulted in THQ **13** as the major product. The formation of this compound can be explained on the basis of a transimination reaction converting **6** and **7** into imine **14**, followed by reaction of the latter to give THQ **13**.[39] To confirm its structure, this THQ was independently synthesized from **2** by use of an excess of 2-methylpropanal and MeOH as the nucleophile.

^{1}H NMR analysis of the obtained THQs **9**−**13** showed that they were contaminated by variable amounts (5−20%) of the starting imines. In order to complete the reaction sequence and to isolate pure, polymer-free THQs, compounds **9**−**13** were subjected to reductive desulfurization with $NaBH_4/NiCl_2$ (Scheme 4).[40] This reaction, carried out in a MeOH/THF (3:1) mixture as solvent for 72 h at room temp., permitted the traceless removal of THQs **15**−**19** from the polymer. These compounds were obtained as single *cis* isomers[41] in 21 to 48% overall yields from the corresponding imines (Table 1).[42]

The yields of each of the two steps necessary for converting the imines into PEG-free THQs were tentatively established at ca. 60−70% on the basis of ^{1}H NMR analysis of the crude PEG-supported THQs and on the yields of the desulfurization reactions carried out on some nonsupported and closely related model compounds.

The possibility of introducing different substituents at C-4 was then studied by performing the $Yb(OTf)_3$-catalyzed reaction between imine **3** and 2-methylpropanal (2 mol-equiv.) in the presence of different nucleophiles (3 mol-



Scheme 4. Synthesis of PEG-supported THQs **20**−**22** and traceless removal of THQs **15**−**19**, **23**, and **24**

Table 1. Synthesis of THQs **15**−**19**, **23**, and **24** by three-and four-component condensation

Imine	R	R^1H[a]	PEG-THQ	THQ	Yield (%)[b]
3	Ph	MeOH	**9**	**15**	46
4	4-FC_6H_4	MeOH	**10**	**16**	48
5	2-furyl	MeOH	**11**	**17**	21
8	CO_2Et	EtOH	**12**	**18**	41
14	*i*Pr	MeOH	**13**	**19**	25
3	Ph	BnOH	**20**	**23**	56
3	Ph	PhSH	**21**	**24**	41
3	Ph	2-PySH	**22**	**15**	44
3[c]	Ph	MeOH	**9**	**15**	44
4[c]	4-FC_6H_4	MeOH	**10**	**16**	46
3[c]	Ph	BnOH	**20**	**23**	47

[a] When R^1H = MeOH, the reaction was carried out in MeOH as solvent; with different nucleophiles, the reaction solvent was DCM. [b] Isolated overall yields (see text). The products were obtained as single *cis* isomers. [c] Four-component condensation (see text).

equiv.). Use of benzyl alcohol, thiophenol, and 2-pyridylthiol resulted in the formation of the PEG-supported THQs **20**−**22**, isolated, as before, as crude products (Scheme 4). The reductive desulfurization of these compounds resulted in the isolation of PEG-free THQs, the structures of which depended on the nature of the residue at C-4 (Scheme 4 and Table 1).

Starting from 4-benzyloxy-substituted THQ **20**, compound **23** was isolated in 56% overall yield from **3**. Reduction of 4-phenylthio-substituted THQ **21** afforded the expected, fully desulfurized adduct **24** in 41% overall yield. Unexpectedly, however, the same treatment carried out on 4-pyridylthio-substituted compound **22** did not produce the same compound **24**, but afforded the 4-methoxy-substituted THQ **15** in 44% overall yield. This surprising behavior was also observed when the nonsupported analog of **22**, namely **25**,[28] underwent reaction with $NaBH_4/NiCl_2$ in MeOH/THF (3:1) at room temp. to give the substituted product **15** in 72% yield and the reduction product **24** in only 10% yield.[43]

Finally, the possibility of performing this soluble polymer-supported synthesis of THQs by means of a four-component reaction was investigated. We were pleased to find that when a mixture of amine **2**, benzaldehyde or 4-fluorobenzaldehyde (3 mol-equiv.), 2-methylpropanal (2 mol-equiv.), and $Yb(OTf)_3$ (0.3 mol-equiv.) was treated in MeOH at room temp. for 96 h or at reflux for 24 h the PEG-supported THQs **9** and **10** were isolated. The same reaction carried out with benzaldehyde and benzyl alcohol similarly gave adduct **20**. Reductive desulfurization of these crude products provided the nonsupported THQs **15** (44%), **16** (46%), and **23** (47%) in yields only slightly lower than those observed in the preparation of the same compounds from the pre-formed imines.

Conclusions

In conclusion, a 4-alkylthio-substituted aniline anchored on a modified PEG has easily been synthesized in very high yield from the monomethyl ether of poly(ethylene glycol) of M_w = 5000. Starting from this supported aniline, representative PEG-supported imines have efficiently been prepared by different methods. Some of these imines were employed in three- and four-component, soluble polymer-supported syntheses of 1,2,3,4-tetrahydroquinolines bearing different substituents at C-2 and C-4. The polymer support did not seem to interfere with the THQ synthesis, which proceeded similarly well as its nonsupported counterpart.[28] Traceless removal of the THQs from the PEG-support was accomplished by a reductive desulfurization reaction, which completed the transformation of the supported aniline into the released THQ in 40−50% overall yield for the imine formation, THQ synthesis, and traceless removal sequence.

Experimental Section

General: ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$ solutions and were referenced to tetramethylsilane (TMS) at δ = 0.00. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to δ = 77.0 in [D]chloroform ($CDCl_3$). IR spectra were recorded on thin films or as solutions in CH_2Cl_2. All the PEG samples were melted at 80 °C under vacuum for 30 min before use, to remove traces of moisture. After the reaction, PEG-supported product purification involved evaporation of the reaction solvent in vacuum and addition of the residue, dissolved in a few mL of CH_2Cl_2, to diethyl ether (50 mL g^{-1} of polymer), which was stirred and cooled at 0 °C. After 20−30 min of stirring at 0 °C, the obtained suspension was filtered through a sintered glass filter, and the solid was repeatedly washed on the filter with diethyl ether (up to 100 mL/g of polymer, overall).

Yields and Purity Determination of PEG-Supported Compounds: The yields of the PEG-supported compounds were determined by weight, on the assumption that M_w for the PEG fragment was

5000 Da. (The M_w actually ranged from 4500 to 5500.) The indicated yields were for pure compounds. The purities of these compounds were determined by ^{1}H NMR analysis in $CDCl_3$ at 300 MHz with presaturation of the methylene signals of the polymer centered at δ = 3.63. When recording the NMR spectra, a relaxation time of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of the integration. The relaxation delay was selected after T_1 measurements. The integrals of the signals of the PEG CH_2OCH_3 fragment at δ = 3.30 and 3.36 were used as internal standard. The estimated integration error was ± 5%. In all of the compounds reported here, the aromatic protons of the *para*-disubstituted rings are described, for sake of simplicity, as AB systems. Since their J_{meta} values are not zero they are in fact more complex A′A′B′B′ systems.[44]

Synthesis of Amine 2: Potassium carbonate (4 mol-equiv.) and 4-aminothiophenol (2 mol-equiv.) were added to a stirred 0.1−0.5 M solution of mesylate **1**[10] (2−20 g, ca. 0.4−4.0 mmol) in dry DMF. The resulting mixture was stirred at 60 °C for 40 h. After removal of the solvent under reduced pressure, the residue was taken up in DCM and the resulting solution was washed with diluted NaOH. The organic phase was separated, dried with sodium sulfate, filtered, and concentrated to a small volume. After precipitation and filtration (see above) the product was obtained in quantitative yield. ^{1}H NMR: δ = 7.20 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to S in Ar), 7.07 (B part of an AB system, 2 H, *J* = 8.0 Hz, H *meta* to O in Ar), 6.80 (A part of an AB system, 2H *J* = 8.0 Hz, H *ortho* to O in Ar), 6.56 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to S in Ar), 4.09 (t, *J* = 7.5 Hz, 2 H, PEGCH_2OAr), 2.67 (t, *J* = 7.4 Hz, 2 H, ArCH_2), 2.60 (t, *J* = 7.0 Hz, 2 H, CH_2S), 2.30 (br s, 2 H, NH_2),1.77 (m, 2 H, $CH_2-CH_2-CH_2$).

Synthesis of Imines 3−5: A mixture of amine **2** (1.0−5.0 g, ca. 0.2−1.0 mmol) and neat aldehyde (5 mol-equiv.) was stirred at 80−90 °C for 12−24 h. The cooled mixture was then dissolved in the minimum amount of DCM and the polymer was precipitated as described above.

Imine 3: 97% yield. ^{1}H NMR: δ = 8.47 (s, 1 H, *CH*=N), 7.90 (d, *J* = 7.5 Hz, 2 H, 2 H of N=CH-*Ph*), 7.48 (m, 3 H, 3H of N=CH-*Ph*), 7.35 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to S in Ar), 7.17 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O in Ar), 7.08 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O in Ar), 6.84 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to S in Ar), 4.09 (t, *J* = 7.5 Hz, 2 H, PEGCH_2OAr), 2.91 (t, *J* = 7.5 Hz, 2 H, ArCH_2), 2.70 (t, *J* = 7.5 Hz, 2 H, CH_2S),1.95 (m, 2 H, $CH_2-CH_2-CH_2$).

Imine 4: 96% yield. ^{1}H NMR: δ = 8.41 (s, 1 H, *CH*=N), 7.90 (dd, *J* = 5.5, 8.0 Hz, 2 H, 2 H of N=CH-*Ar*), 7.32 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to S in Ar), 7.12 (m, 4 H, H *meta* to O in Ar and 2 H of CH=N-*Ar*), 7.09 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O in Ar), 6.82 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to S in Ar), 4.09 (t, *J* = 7.5 Hz, 2 H, PEGCH_2OAr), 2.89 (t, *J* = 7.5 Hz, 2 H, ArCH_2), 2.68 (t, *J* = 7.5 Hz, 2 H, CH_2S), 1.90 (m, 2 H, $CH_2-CH_2-CH_2$).

Imine 5: 95% yield. ^{1}H NMR: δ = 8.31 (s, 1 H, *CH*=N), 7.64 (br. s, 1 H, 1 H of furyl residue), 7.33 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to S in Ar), 7.19 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O in Ar), 7.09 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O in Ar), 6.97 (d, *J* = 3.1 Hz, 1 H, 1 H of furyl residue), 6.85 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to S in Ar), 6.58 (dd, *J* = 1.8, 3.1 Hz, 1 H, 1 H of furyl residue), 4.09 (t, *J* = 7.5 Hz, 2 H, PEGCH_2OAr), 2.92 (t, *J* = 7.0 Hz, 2 H, ArCH_2), 2.70 (t, *J* = 7.5 Hz, 2 H, CH_2S), 1.95 (m, 2 H, $CH_2-CH_2-CH_2$).

Synthesis of Imines 6 and 7: The appropriate aldehyde (5 mol-equiv.) was added in one portion to a stirred 0.2 M solution of amine **2** (1.0−5.0 g, ca. 0.2−1.0 mmol) in a mixture of DCM/trimethyl orthoformate (30:70). The mixture was stirred at room temp. for 43 h, the solvent was evaporated under vacuum, the residue was dissolved in the minimum amount of DCM, and the polymer was precipitated.

Imine 6: 95% yield. ^{1}H NMR: δ = 7.80 (d, *J* = 4.0 Hz, 1 H, *CH*=N), 7.31 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to S in Ar), 7.16 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O in Ar), 6.95 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O in Ar), 6.85 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to S in Ar), 4.09 (t, *J* = 7.5 Hz, 2 H, PEGCH_2OAr), 2.85 (t, *J* = 7.0 Hz, 2 H, ArCH_2), 2.63 (t, *J* = 7.5 Hz, 2 H, CH_2S), 2.40 (m, 1 H, *CH* of cyclohexyl group), 2.05 −1.80 (m, 8 H, $CH_2-CH_2-CH_2$ and 6 H of cyclohexyl group), 1.43−1.17 (m, 4 H, remaining H of cyclohexyl group).

Imine 7: 96% yield. ^{1}H NMR: δ = 7.75 (d, *J* = 2.0 Hz, 1 H, *CH*=N), 7.28 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to S in Ar), 7.16 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O in Ar), 6.95 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O in Ar), 6.85 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to S in Ar), 4.65 (m, 1 H, CH_2-CH-O), 4.21 (dd, *J* = 5.5 Hz, 1 H, one H of CH_2−CH−O), 4.09 (t, *J* = 7.5 Hz, 2 H, PEGCH_2OAr), 4.04 (m, 1 H, one H of CH_2−CH−O), 2.90 (t, *J* = 7.0 Hz, 2 H, ArCH_2), 2.63 (t, *J* = 7.5 Hz, 2 H, CH_2S), 1.95 (m, 2 H, $CH_2-CH_2-CH_2$), 1.70−1.33 (m, 10 H, H of cyclohexylidene group).

Synthesis of Imine 8: A commercially available 50% solution of ethyl glyoxylate in toluene (3 mol-equiv.) was added to a stirred suspension of amine **2** (1.0−2.0 g, ca. 0.2−0.4 mmol) in toluene (5−10 mL). The mixture was stirred at 110 °C for 24 h. The solvent was then evaporated under reduced pressure, the residue was dissolved in the minimum amount of DCM, and the polymer was precipitated to afford the product in 95% yield. ^{1}H NMR: δ = 7.90 (s, 1 H, *CH*=N), 7.28 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to S in Ar), 7.16 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O in Ar), 6.95 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O in Ar), 6.85 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to S in Ar), 4.35 (q, *J* = 7.0 Hz, 2 H, O−CH_2−CH_3), 4.09 (t, *J* = 7.5 Hz, 2 H, PEGCH_2OAr), 2.95 (t, *J* = 7.0 Hz, 2 H, ArCH_2), 2.63 (t, *J* = 7.5 Hz, 2 H, CH_2S), 1.95 (m, 2 H, $CH_2-CH_2-CH_2$), 1.35 (t, *J* = 7.0 Hz, 3 H, O−CH_2−CH_3).

Three-Component Synthesis of PEG-Supported THQ: Freshly distilled 2-methylpropanal (2 mol-equiv.) and $Yb(OTf)_3$ (0.3 mol-equiv.) were added to a stirred 0.1 M solution of imine (1.0−2.0 g, ca. 0.2−0.4 mmol) in dry MeOH, and the mixture was stirred at room temp. for 96 h or at reflux for 24 h. With other nucleophiles, DCM was used as reaction solvent and 3 mol-equiv. of nucleophile were employed. A small amount of activated carbon was then added, and the resulting mixture was stirred for 5 min and then filtered through a Celite cake. The solvent was then evaporated under vacuum, the residue was dissolved in the minimum amount of DCM, and the polymer was precipitated to afford the crude product.

Four-Component Synthesis of PEG-Supported THQ: Freshly distilled aromatic aldehyde (3 mol-equiv.), 2-methylpropanal (2 mol-equiv.), and $Yb(OTf)_3$ (0.3 mol-equiv.) were added − in that order

− to a stirred 0.1 M solution of amine **2** (1.0−2.0 g, ca. 0.2−0.4 mmol) in dry MeOH, and the mixture was stirred either at room temp. for 96 h or at reflux for 24 h. When benzyl alcohol was the nucleophile, DCM was used as reaction solvent and 3 mol-equiv. of nucleophile were employed. The reaction was then worked up as described before to afford the crude product.

PEG-THQ 9: ^{1}H NMR: δ = 7.43−7.27 (m, 6 H, 5 H of CH-*Ph* and 7-H), 7.21 (d, *J* = 1.8 Hz, 1 H, 5-H), 7.06 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O), 6.83 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O), 6.53 (d, *J* = 7.8 Hz, 1 H, 8-H), 4.53 (s, 1 H, 2-H), 4.09 (t, *J* = 7.5 Hz, 2 H, PEG*CH*$_2$OAr), 3.36 (s, 3 H, MeO group at C-4), 2.80 (t, *J* = 7.4 Hz, 2 H, *CH*$_2$Ar), 2.67 (t, *J* = 7.4 Hz, 2 H, *CH*$_2$S), 1.90 (m, 2 H, CH$_2$−*CH*$_2$−CH$_2$), 0.93 (s, 3 H, Me at C-3), 0.67 (s, 3 H, Me at C-3). The 4-H proton signal overlapped with the PEG signals.

PEG-THQ 10: ^{1}H NMR: δ = 7.41 (dd, *J* = 5.5, 8.5 Hz, 2 H, 2 H of the fluorinated Ar), 7.28 (dd, *J* = 7.8, 1.8 Hz, 1 H, 7-H), 7.21 (d, *J* = 1.8 Hz, 1 H, 5-H), 7.12−7.04 (m, 4 H, 2 H B part of an AB system and 2 H of the fluorinated Ar), 6.83 (A part of an AB system, 2 H, *J* = 8.5 Hz, 2 H, H *meta* to O), 6.53 (d, *J* = 7.8 Hz, 1 H, 8-H), 4.53 (s, 1 H, 2-H), 3.36 (s, 3 H, methoxy group at C-4), 4.09 (t, *J* = 7.5 Hz, 2 H, PEG*CH*$_2$OAr), 3.36 (s, 3 H, MeO group at C-4), 2.77 (t, *J* = 7.5 Hz, 2 H, *CH*$_2$Ar), 2.68 (t, *J* = 7.5 Hz, 2 H, *CH*$_2$S), 1.87 (m, 2 H, CH$_2$−*CH*$_2$−CH$_2$), 0.91 (s, 3 H, Me at C-3), 0.64 (s, 3 H, Me at C-3). The 4-H proton signal overlapped with the PEG signals.

PEG-THQ 11: ^{1}H NMR: This compound gave a poorly resolved spectrum that prevented a reliable peak assignment.

PEG-THQ 12: ^{1}H NMR: δ = 7.17 (dd, *J* = 7.8, 1.7 Hz, 1 H, 7-H), 7.12−7.04 (m, 3 H, 2 H B part of an AB system and 5-H), 6.82 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O), 6.57 (d, *J* = 7.8 Hz, 1 H, 8-H), 4.40 (q, *J* = 6.7 Hz, 2 H, COO*CH*$_2$Me), 4.26 (s, 1 H, 2-H), 4.09 (t, *J* = 7.5 Hz, 2 H, PEG*CH*$_2$OAr), 2.77 (t, *J* = 7.5 Hz, 2 H, *CH*$_2$Ar), 2.67 (t, *J* = 7.5 Hz, 2 H, *CH*$_2$S), 1.93 (m, 2 H, CH$_2$−*CH*$_2$−CH$_2$), 1.42 (t, *J* = 6.7 Hz, 3 H, CO-OCH$_2$*Me*), 1.33 (s, 3 H, Me at C-3), 1.13 (s, 3 H, Me at C-3), 1.11 (t, 3H *J* = 6.5 Hz, *Me* of ethoxy group at C-4). The 4-H and O*CH*$_2$Me proton signals overlapped with the PEG signals.

PEG-THQ 13: ^{1}H NMR: δ = 7.23 (dd, *J* = 7.8, 1.7 Hz, 1 H, 7-H), 7.16 (d, *J* = 1.7 Hz, 1 H, 5-H), 7.05 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O), 6.82 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O), 6.50 (d, *J* = 7.8 Hz, 1 H, 8-H), 4.09 (t, *J* = 7.5 Hz, 2 H, PEG*CH*$_2$OAr), 3.31 (s, 3 H, methoxy group at C-4), 3.27 (d, *J* = 5.7 Hz, 1 H, 2-H), 2.75 (t, *J* = 7.4 Hz, 2 H, *CH*$_2$Ar), 2.67 (t, *J* = 7.4 Hz, 2 H, *CH*$_2$S), 2.10 (m, 1 H, CH of *i*Pr group), 1.87 (m, 2 H, CH$_2$−*CH*$_2$−CH$_2$), 1.14 (s, 3 H, Me at C-3), 1.08 (d, *J* = 6.5 Hz, 3 H, one Me of *i*Pr group), 1.00 (d, *J* = 6.5 Hz, 3 H, one Me of *i*Pr group), 0.74 (s, 3 H, Me at C-3).

PEG-THQ 20: ^{1}H NMR: δ = 7.43−7.27 (m, 11 H, H atoms of 2 Ph groups and 7-H), 7.19 (d, *J* = 1.7 Hz, 1 H, 5-H), 7.05 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O), 6.79 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O), 6.53 (d, *J* = 8.2 Hz, 1 H, 8-H), 4.66 (s, 1 H, 2-H), 4.61 (B part of an AB system, 1 H, *J* = 12.0 Hz, 1 H of O*CH*$_2$Ph), 4.49 (A part of an AB system, 1 H, *J* = 12.0 Hz, 1 H of O*CH*$_2$Ph), 4.09 (t, *J* = 7.5 Hz, 2 H, PEG*CH*$_2$OAr), 2.77 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$Ar), 2.68 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$S), 1.87 (m, 2 H, CH$_2$−*CH*$_2$−CH$_2$), 0.99 (s, 3 H, Me at C-3), 0.66 (s, 3 H, Me at C-3). The 4-H proton signal overlapped with the PEG signals.

PEG-THQ 21: ^{1}H NMR: δ = 7.45−7.05 (m, 12 H, 10 H of the 2 Ph groups, and 5-H and 7-H) 7.05 (B part of an AB system, 2 H, *J* = 8.5 Hz, H *ortho* to O), 6.78 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O), 6.55 (d, *J* = 8.5 Hz, 1 H, 8-H), 4.65 (s, 1 H, 2-H), 4.15 (s, 1 H, 4-H), 4.09 (t, *J* = 7.5 Hz, 2 H, PEG*CH*$_2$OAr), 2.83 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$Ar), 2.66 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$S), 1.87 (m, 2 H, CH$_2$−*CH*$_2$−CH$_2$), 0.90 (s, 3 H, Me at C-3), 0.75 (s, 3 H, Me at C-3).

PEG-THQ 22: ^{1}H NMR: δ = 8.47 (d, *J* = 5.2 Hz, 1 H, H α to N in pyridine ring), 7.55−7.35 (m, 6 H, 3 H of pyridine ring, 2 H of Ph ring, 1 H of the aromatic part of the THQ moiety), 7.17−7.00 (m, 6 H, 3 H of Ph group, 1 H of the aromatic part of THQ moiety, 2 H of the B part of the AB system), 6.80 (A part of an AB system, 2 H, *J* = 8.5 Hz, H *meta* to O), 6.48 (d, *J* = 8.2 Hz, 1 H, 8-H), 5.32 (s, 1 H, 4-H), 4.47 (s, 1 H, 2-H), 4.09 (t, *J* = 7.5 Hz, 2 H, PEG*CH*$_2$OAr), 2.70 (t, *J* = 7.0 Hz, 2 H, PEG*CH*$_2$SAr), 2.60 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$Ar), 1.77 (m, 2 H, CH$_2$−*CH*$_2$−CH$_2$), 1.00 (s, 3 H, Me at C-3), 0.90 (s, 3 H, Me at C-3).

General Procedure for the Desulfurization Reaction: $NiCl_2 \cdot 6H_2O$ (15 mol equiv.) was added in one portion to a stirred suspension of crude PEG-THQ in a mixture of MeOH/THF (3:1) (5 mL/g of PEG-THQ). The mixture was then cooled to 0 °C, and $NaBH_4$ (45 mol-equiv.) was added portionwise. The resulting black mixture was stirred at room temp. for 96 h and was then filtered through a Celite cake. The filtrate was concentrated under vacuum, and the residue was dissolved in the minimum amount of DCM. PEG was then precipitated as usual and filtered off. The solid was thoroughly washed with diethyl ether, and the filtrate was dried with sodium sulfate, filtered, and concentrated under vacuum. The residue thus obtained was purified by flash chromatography with a mixture of hexane/diethyl ether (90:10; 50:50 in the case of **18**) as eluent. The products were obtained in the yields reported in Table 1.

4-Methoxy-3,3-dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline (15): This compound was a viscous oil that melted around room temperature. When starting from 1.0 g of imine **3**, 23.1 mg (46%) of the product was obtained. ^{1}H NMR: δ = 7.47 (d, *J* = 7.8 Hz, 2 H, 2 H of Ph group), 7.33 (m, 3 H, 3 H of Ph group), 7.17 (m, 2 H, 5-H and 7-H), 6.67 (t, *J* = 7.8 Hz, 1 H, 6-H), 6.60 (d, *J* = 7.8 Hz, 1 H, 8-H), 4.58 (s, 1 H, 2-H), 4.25 (br. s, 1 H, NH), 3.57 (s, 1 H, 4-H), 3.41 (s, 3 H, MeO), 0.97 (s, 3 H, Me at C-3), 0.72 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 143.8, 140.4, 131.0, 130.8, 129.0, 127.8, 127.6, 118.5, 115.7, 113.7, 85.2, 59.8, 56.5, 35.8, 23.5, 19.0. $C_{18}H_{21}NO$ (267.4): calcd. C 80.86, H 7.92, N 5.24; found C 81.07, H 7.79, N 5.15.

2-(4-Fluorophenyl)-4-methoxy-3,3-dimethyl-1,2,3,4-tetrahydroquinoline (16): This compound was a viscous pale yellow oil. When starting from 1.0 g of imine **4**, 25.6 mg (48%) of the product was obtained. ^{1}H NMR: δ = 7.43 (dd, *J* = 7.8, 5.5 Hz, 2 H, H *meta* to F in 4-fluorophenyl ring), 7.15 (m, 2 H, 5-H and 7-H), 7.06 (t, 2 H, *J* = 7.8, H *ortho* to F in 4-fluorophenyl ring), 6.68 (t, *J* = 7.8 Hz, 1 H, 6-H), 6.62 (d, *J* = 7.8 Hz, 1 H, 8-H), 4.56 (s, 1 H, 2-H), 4.20 (br. s, 1 H, NH), 3.56 (s, 1 H, 4-H), 3.40 (s, 3 H, MeO), 0.94 (s, 3 H, Me at C-3), 0.69 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 162.5, 144.0, 137.0, 131.1, 130.3, 129.1, 118.6, 115.9, 114.7, 113.8, 85.0, 59.1, 56.5, 35.8, 23.3, 19.0. $C_{18}H_{20}FNO$ (285.4): calcd. C, 75.76, H 7.06, N 4.91; found C 75.49, H 6.98, N 5.03.

2-(2-Furyl)-4-methoxy-3,3-dimethyl-1,2,3,4-tetrahydroquinoline (17): This compound was a viscous pale yellow oil. When starting from 1.0 g of imine **5**, 10.1 mg (21%) of the product was obtained. ^{1}H NMR: δ = 7.42 (d, *J* = 1.5 Hz, 1 H, 5-H in furyl group), 7.13 (dt, *J* = 7.8, 1.0 Hz, 1 H, 7-H), 7.12 (dd, *J* = 7.8, 1.0 Hz, 1 H, 5-

H), 6.68 (dt, J = 7.8, 1.0 Hz, 1 H, 6-H), 6.60 (d, J = 8.0 Hz, 1 H, C-8 H), 6.40 (dd, J = 1.5, 3.2 Hz, 1 H, 4-H in furyl group), 6.34 (d, J = 3.2 Hz, 1 H, 3-H in furyl group), 4.64 (s, 1 H, 2-H), 4.20 (br. s, 1 H, NH), 3.58 (s, 1 H, 4-H), 3.39 (s, 3 H, MeO), 1.03 (s, 3 H, Me at C-3), 0.79 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 151.0, 144.0, 143.6, 131.2, 129.2, 118.8, 116.2, 114.0, 110.2, 108.1, 84.8, 56.7, 54.4, 38.5, 23.0, 19.9. $C_{16}H_{19}NO_2$ (257.3): calcd. C 74.68, H 7.44, N 5.44; found C 74.86, H 7.63, N 5.31.

Ethyl 4-Ethoxy-3,3-dimethyl-1,2,3,4-tetrahydroquinolinye-2-carboxylate (18): This compound was a pale yellow oil. When starting from 1.0 g of imine **8**, 21.3 mg (41%) of the product was obtained. IR: ν̃ = 3400, 1728, 1614, 1465, 1265 cm $^{-1}$.^{1}H NMR: δ = 7.13 (t, J = 7.5 Hz, 1 H, 7-H), 7.03 (d, J = 7.5 Hz, 1 H, 5-H), 6.67 (m, 2 H, 6-H and 8-H), 4.30 (q, J = 7.0 Hz, 2 H, CH_2 of ethoxycarbonyl group), 4.19 (s, 1 H, 2-H), 4.10 (br. s, 1 H, NH), 3.61 (s, 1 H, 4-H), 3.55−3.65 (m, 1 H, 1 H of CH_2 of ethoxy group at C-4), 3.35−3.45 (m, 1 H, 1 H of CH_2 of ethoxy group at C-4), 1.35 (t, J = 7.0 Hz, 3 H, *Me* of ethoxycarbonyl group), 1.31 (s, 3 H, Me at C-3), 1.17 (t, J = 7.0 Hz, 3 H, *Me* of ethoxy group at C-4), 0.69 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 171.3, 144.9, 141.3, 130.5, 128.0, 119.6, 116.0, 80.5, 64.5, 58.6, 56.8, 36.0, 23.6, 22.4, 22.0, 19.5. $C_{16}H_{23}NO_3$ (277.4): calcd. C 69.29, H 8.36, N 5.05; found C 69.11, H 8.51, N 4.98.

4-Methoxy-3,3-dimethyl-2-(1-methylethyl)-1,2,3,4-tetrahydroquinoline (19): This compound was a pale yellow oil. When starting from 1.0 g of imine **14**, 11.0 mg (25%) of the product was obtained. ^{1}H NMR: δ = 7.10 (t, J = 7.5 Hz, 1 H, 7-H), 7.03 (d, J = 7.5 Hz, 1 H, 5-H), 6.61 (m, 2 H, 6-H and 8-H), 4.20 (br. s, 1 H, NH), 3.37 (s, 1 H, 4-H), 3.35 (s, 3 H, MeO), 3.27 (d, J = 2.5 Hz, 1 H, 2-H), 2.12 (m, 1 H, C*H* of *i*Pr group), 1.16 (s, 3 H, Me at C-3), 1.11 (d, J = 7.0 Hz, 3 H, one Me of *i*Pr group), 1.02 (d, J = 7.0 Hz, 3 H, one Me of *i*Pr group), 0.77 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 143.5, 141.0, 129.5, 127.9, 118.1, 112.9, 60.5, 57.5, 54.0, 36.5, 35.0, 23.7, 23.6, 23.3, 17.6. $C_{15}H_{23}NO$ (PM 233.4): calcd. C, 77.21, H 9.93, N 6.00; found C 77.08, H10.07, N 5.90.

3,3-Dimethyl-2-phenyl-4-phenylmethoxy-1,2,3,4-tetrahydroquinoline (23): This compound had a m.p. of 136−138 °C. When starting from 1.0 g of imine **3**, 36.0 mg (56%) of the product was obtained. ^{1}H NMR: δ = 7.50−7.27 (m, 10 H, H atoms of the Ph groups), 7.20 (t, J = 7.5 Hz, 1 H, 7-H), 7.12 (d, J = 7.5 Hz, 1 H, 5-H), 6.70 (t, J = 7.5 Hz, 1 H, 6-H) 6.61 (d, J = 7.5 Hz, 1 H, 8-H), 4.71 (s, 1 H, 2-H), 4.69 (B part of an AB system, 1 H, J = 12.0 Hz, one H of OCH_2Ph), 4.54 (A part of an AB system, 1 H, J = 12.0 Hz, one H of OCH_2Ph), 4.20 (br s, 1 H, NH), 3.83 (s, 1 H, 4-H), 1.00 (s, 3 H, Me at C-3), 0.70 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 144.4, 140.6, 139.0, 131.2, 129.0, 128.9, 128.5, 127.8, 127.7, 127.6, 127.4, 118.6, 115.7, 113.8, 82.3, 69.7, 59.9, 35.9, 23.8, 19.4. $C_{24}H_{25}NO$ (343.5): calcd. C 83.93, H 7.34, N 4.08; found C 84.07, H7.48, N 4.00.

3,3-Dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline (24): This compound was a viscous oil. When starting from 1.0 g of imine **3**, 19.6 mg (44%) of the product was obtained. ^{1}H NMR: δ = 7.35−7.20 (m, 5 H, H atoms of Ph group), 7.02 (m, 2 H, 5-H and 7-H), 6.67 (t, J = 7.5 Hz, 1 H, 6-H) 6.55 (d, J = 7.5 Hz, 1 H, 8-H), 4.22 (br. s, 1 H, NH), 4.18 (s, 1 H, 2-H), 2.77 (B part of an AB system, 1 H, J = 15.8 Hz, one of 4-H), 2.53 (A part of an AB system, 1 H, J = 15.8 Hz, one of 4-H), 0.97 (s, 3 H, Me at C-3), 0.87 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 141.9, 139.5, 131.8, 129.7, 128.4, 127.6, 126.9, 117.1, 115.5, 113.3, 65.4, 41.9, 31.9, 28.0, 21.9. $C_{17}H_{19}N$ (PM 237.3): calcd. C 86.03, H 8.07, N 5.90; found C 85.91, H 7.99, N 5.99.

3,3-Dimethyl-2-phenyl-4-(2-pyridylthio)-1,2,3,4-tetrahydroquinoline (25): This compound had a m.p. of 58−60 °C, and was prepared in 72% yield (0.1214 g) from the *N*-phenylimine of benzaldehyde (0.090 g, 0.5 mmol) as previously described.[28] ^{1}H NMR: δ = 8.50 (d, J = 5.2 Hz, 1 H, 6-H in pyridine ring), 7.50−7.20 (m, 8 H, 3-H and 4-H of pyridine ring, 5 H of Ph ring, 5-H of the THQ moiety), 7.08−7.00 (m, 2 H, 4-H in pyridine ring, 7-H of the THQ moiety), 6.70 (m, 1 H, 6-H), 6.57 (d, J = 8.2 Hz, 1 H, 8-H), 5.41 (s, 1 H, 4-H), 4.52 (s, 1 H, 2-H), 4.24 (br s, 1 H, NH), 1.04 (s, 3 H, Me at C-3), 0.94 (s, 3 H, Me at C-3). ^{13}C NMR: δ = 158.9, 149.0, 143.0, 140.2, 136.0, 130.6, 128.8, 128.2, 127.8, 127.6, 122.1, 121.3, 119.6, 117.3, 113.6, 61.5, 52.7, 36.9, 24.3, 21.0. $C_{22}H_{22}N_2S$ (346.5): calcd. C 76.26, H 8.06, N 6.40; found C 76.07, H 7.97, N 6.53.

Acknowledgments

We thank the MURST (Progetto Nazionale Stereoselezione in Sintesi Organica − Metodologie e Applicazioni) and the CNR for financial support.

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[41] Minor amounts ($\leq$ 10%) of the *trans* isomers were observed when the reduction was performed on PEG-THQ obtained after prolonged reaction times.
[42] Since the imines were, in their turn, obtained in nearly quantitative fashion from amine **2**, these are indeed overall yields for the **2** to **15**−**19** transformation. On the basis of desulfurization reactions carried out on some nonsupported model compounds, the yield of the THQ removal from PEG was tentatively established at ca. 70%.
[43] Since THQ **21** (see above) behaved as expected under the reductive desulfurization conditions, it is tempting to ascribe the unusual course of the reduction of THQ **22** to the presence of the 2-pyridylthio substituent at C-4 in this compound. It can be surmised that the metal-coordinating nature of the 2-pyridyl residue can promote the substitution of the 2-pyridylthiolate ion, an excellent leaving group, by the methoxide ion probably present in the reduction reaction medium. Obviously, this hypothesis holds true only if the substitution process is faster then the reduction reaction, which apparently involves a better nucleophile (hydride vs. methoxide ion).
[44] We thank one of the referees for bringing this point to our attention.

Received October 6, 2001
[O01484]