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A Novel Solid Support for Derivatization and Subsequent *N*-Alkylation of Secondary Amines: Preparation of *N*-Alkylated 5- and 6-Alkoxy-1,2,3,4-tetrahydroisoquinolines *via* Mitsunobu Reaction

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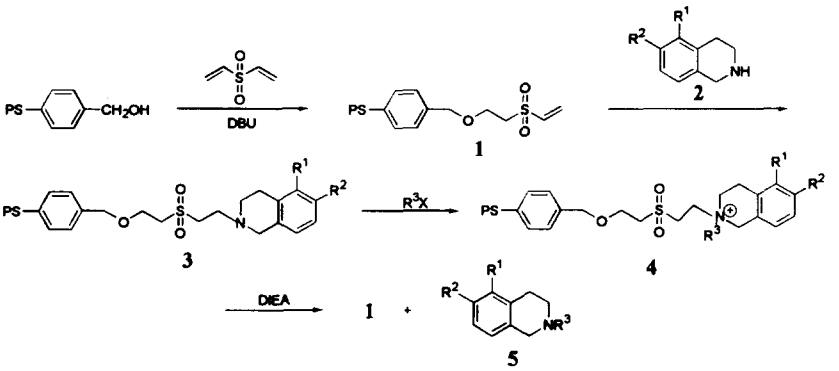
Abstract: A hydroxymethylated polystyrene resin has been converted to its vinylsulfonylethyl ether (**1**) by DBU catalyzed addition of the hydroxy groups to divinyl sulfone. The support obtained was used to convert 5- and 6-(tetrahydropyran-2-yloxy)-1,2,3,4-tetrahydroisoquinolines to a set of *N*-alkylated tetrahydroisoquinolines bearing various 5- and 6-alkoxy substituents (**5a-m**). The synthesis involved attachment of the starting material to the support by Michael addition, acid-catalyzed removal of the tetrahydropyranyl protection, Mitsunobu etherification, quaternarization with alkyl amines, and release in solution with diisopropylethylamine. © 1997 Elsevier Science Ltd.

The solid phase synthesis of combinatorial libraries by computer controlled robots has become a routine techinque to obtain lead compounds for drug development.[1] The early emphasis has been on combinatorial assembly of large oligomeric compounds, such as peptides, peptoids and oligonucleotides, and their complex mixtures have been used in screening of the bioaffinity. More limited libraries of relatively small organic molecules that are prepared in a parallel mode have recently gained increasing popularity. Even the latter syntheses are usually carried out by using solid supports and linkers adopted from peptide or oligonucleotide chemistry,[2] which inevitably restricts the choice of reactions applicable to the construction of the library. We now show that conversion of a hydroxymethylated polystyrene resin to its vinylsulfonylethyl ether (**1**) affords a rather versatile solid support for derivatization of secondary amines (Scheme 1). Michael addition of the amine to the vinylsulfonyl group yields a tertiary amine structure (**3**) that well stands acidic and basic conditions, and may also be expected to tolerate the conditions of numerous transformation reactions at the other functionalities of the attached amine. After the desired derivatization, the amine nitrogen may be quternarized and the tertiary amine is released in solution by Hoffman elimination. An analogous approach based on Michael addition to a resin-bound acrylate ester has recently been described.[3] The carboxylic ester function, however, renders the linker rather susceptible to hydrolysis and other acyl substitutions, in striking contrast to the vinylsulfonyl linker. The applicability of support **1** was verified by preparing a set of *N*-alkyl-5- and -6-alkoxy-1,2,3,4-tetrahydroisoquinolines (**5a-m**), potential ligands of α_2-receptors, *via* addition of 5- or 6-(tetrahydropyran-2-yloxy)-1,2,3,4-tetrahydroisoquinoline to the support, followed by deprotection, Mitsunobu displacement[4], quternarization with various alkyl groups and release with diisopropylethylamine (Scheme 2).

The solid support **1** was obtained by treating the commercial hydroxymethylated polystyrene beads (Sigma; 0.2 g) in dry CH_2Cl_2 (3.0 mL) with divinyl sulfone (2.0 mmol) and DBU (0.7 mmol) overnight at room temperature. The beads were washed with CH_2Cl_2 (3×3 mL) and MeOH (3×3 mL), and dried under

reduced pressure prior to use. To determine the loading of vinylsulfonyl groups and to optimize the reaction conditions, 5-ethoxy-1,2,3,4-tetrahydroisoquinoline[5] (2: R^1 = OEt, R^2 = H) was attached to 1 to give 3, quternized with MeI to 4, and released to solution as 5b with diisopropylethylamine. The attachment of 2 (0.25 mmol) to support 1 (50 mg) was carried out in DMF (4d at room temperature), followed by washings with DMF, CH_2Cl_2 and MeOH (3×3mL each), and drying under reduced pressure. To convert 3 quantitatively to 4 (R^3 = Me), 3 (15 mg) was treated in DMF (1 mL) with MeI (1.6 mmol) from 0.5 to 18 h, and after that again washed and dried as described above. 4 was finally suspended in CH_2Cl_2 (1 mL) containing diisopropylethylamine (0.3 mmol). The amount of 5b released was determined by RP HPLC (Purospher RP-18e; 0.050 mol L^{-1} phosphate buffer, pH 2.0; flow rate 0.75 mL min^{-1}; elution: 0-10 min buffer:MeCN 9:1, 10-30 min gradient to pure MeCN), using an authentic sample[7] of 5b as a standard. These analyses showed that (i) the loading ranged from 200 to 270 μmol g^{-1}, (ii) no UV-absorbing side products were formed, and (iii) rapid quaternarization (0.5 h) gave the highest yields (Table 1).



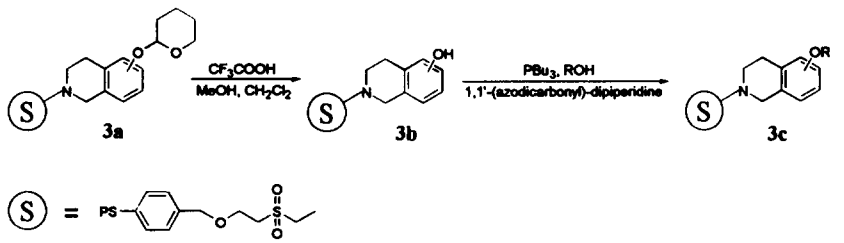
Scheme 1. PS = polystyrene, R^1, R^2 = alkoxy or H, R^3 = alkyl, X = Br, I

Table 1. Reaction times for quaternization of 5-ethoxy-1,2,3,4-tetrahydroisoquinoline on the vinylsulfonyl derivatized solid support 3 (R^1 = OEt, R^2 = H) and release of the tertiary amine (5; R^1 = OEt, R^2 = H, R^3 = Me) to solution.[a]

Entry	Time of quaternisation (h)	Time of release (h)	Yield of 5 (μmol g^{-1})
1	18	18	210
2	18	4	220
3	18	1	240
4	6	18	230
5	1	18	270
6	0.5	0.5	250

[a]The quaternarization was carried out with MeI (1.6 mmol) in DMF (1 mL), and the release with diisopropylethylamine (0.3 mmol) in CH_2Cl_2 (1 mL) at room temperature.

The applicability of support 1 was demonstrated by preparing a small model library of substituted tetrahydroisoquinolines bearing various alkoxy substituents at C5 or C6 and alkyl groups at N2 (**5a-m**). The procedure utilized is outlined in Scheme 2. 5- or 6-(tetrahydropyran-2-yloxy)-1,2,3,4-tetrahydroisoquinoline[8] was attached to solid support 1 to give **3a** (50 mg), and the acetal protection was removed with TFA (2.6 mmol) in a mixture of CH_2Cl_2 and MeOH (1:1, v/v; 2 mL, overnight at rt). The solid phase (**3b**) washed with CH_2Cl_2 and MeOH was then subjected to Mitsunobu reaction to introduce the desired alkoxy substituent. Conventional Mitsunobu reagents, triphenyl phosphine and DEAD, were found to give only a 10% yield, possibly due to liberation of heat upon addition of DEAD. By contrast tributyl phosphine - 1,1'-(azodicarbonyl)dipiperidine approach[10] was successfully applied,[11] leading to 80-90% yields of **5a-m** (Table 2). The quaternarization was carried out with EtI, PrI and BnBr, in addition to MeI. **5a-m** were identified by EI-MS, and by RP HPLC spiking with authentic samples[12] prepared in solution. The yields determined by RP HPLC, using an authentic sample prepared in solution as a standard, ranged from 80 % to 100 % (with the exception of **5c** 40 % and **5d** 25 %).



Scheme 2.

Table 2. The compounds synthesized by solid phase Mitsunobu reaction and subsequent *N*-alkylation on support **1**.

Entry	R^1	R^2	R^3	R_t [a] (min)	EI-MS (*m/z*)
5a	MeO	H	Me	3.2	177
5b	EtO	H	Me	8.1	191
5c	$MeCHCHCH_2O$	H	Me	17.3	217
5d	Me_2CHCH_2O	H	Me	18.0	219
5e	$Ph(CH_2)_4O$	H	Me	20.9	295
5f	H	MeO	Me	2.6	177
5g	H	EtO	Me	5.6	191
5h	H	$MeCHCHCH_2O$	Me	16.6	217
5i	H	Me_2CHCH_2O	Me	17.8	219
5j	H	$Ph(CH_2)_4O$	Me	20.8	295
5k	EtO	H	Et	11.2	204
5l	EtO	H	Pr	16.0	218
5m	EtO	H	$PhCH_2$	18.6	266

[a]Purospher RP-18e; 0.050 mol L^{-1} phosphate buffer, pH 2.0; flow rate 0.75 mL min^{-1}; elution: 0-10 min buffer:MeCN 9:1, 10-30 min gradient to pure MeCN.

REFERENCES AND NOTES

1. For a review see e.g.: a) Gallop, M.A.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gordon, E.M. *J. Med. Chem.* **1994**, 37, 1233, b) DeWitt, S.H.; Czarnik, A.W. *Curr. Opin. Biotechnol.* **1995**, 6, 640.
2. For a review see: Hemkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron* **1996**, 52, 4527.
3. Morphy, R.J.; Rankovic, Z.; Rees, D.C. *Tetrahedron Lett.* **1996**, 37, 3209.
4. Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1967**, 40, 935.
5. 5-Hydroxy-1,2,3,4-tetrahydroisoquinoline[6] was treated in aq. MeCN (50%, v/v) overnight with 1 eqv of di-*tert*-butyl carbonate and NaOH. 2-*tert*-butoxycarbonyl-5-hydroxy-1,2,3,4-tetrahydroisoquinoline obtained was purified by Silica gel chromatography ($MeOH/CH_2Cl_2$ 7:93) and subjected to Mitsunobu reaction[4] in THF (Ph_3P 1.2 eqv., EtOH 1.5 eqv., DEAD 1.2 eqv. dropwise). The resulting 2-*tert*-butoxycarbonyl-5-ethoxy-1,2,3,4-tetrahydroisoquinoline was purified by Silica gel chromatography ($MeOH/CH_2Cl_2$ 1:99), and the *t*-BOC group was removed with ethanolic HCl. The overall yield of **2** (R^1 = OEt, R^2 = H) recrystallized from dry EtOH was 45 %. ^1H NMR (DMSO-d_6, 500 MHz): 7.02 (1H, t, 7.8 Hz), 6.70 (1H, d, 8.0 Hz), 6.57 (1H, d, 7.2 Hz), 3.98 (2H, q, 6.9 Hz), 3.77 (2H, s), 3.24 (2H, s), 2.91 (2H, s), 1.31 (3H, t, 6.9 Hz); ^{13}C NMR (DMSO-d_6, 120 MHz): 156.1, 137.5, 125.7, 123.5, 118.1, 108.2, 62.9, 47.7, 43.0, 23.1, 14.7; MS(EI$^+$): 177 (95%, M^+), 148 (100%), 132 (25%), 120 (43%), 104 (56%), 91 (33%).
6. Durand, S.; Lusinchi, X.; Moreau, R.C. *Bull. Soc. Chim. France* **1961**, *207*, 270.
7. Prepared by Mitsunobu reaction[4] from 5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[6] (Ph_3P 1.2 eqv., EtOH 1.5 eqv., DEAD 1.2 eqv dropwise in THF), purifiead by Silica gel chromathography ($MeOH/CH_2Cl_2$) (System E) and recrystallised from dry EtOH. Yield 48%. ^1H NMR ($CDCl_3$, 400 MHz): 7.07 (1H, t, 8.1 Hz), 6.64 (2H, m), 4.01 (2H, q, 7.1 Hz), 3.55 (2H, s), 2.81 (2H, t, 6.1 Hz), 2.67 (2H, t, 6.1 Hz), 2.44 (3H, s), 1.40 (3H, t, 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.5, 135.9, 126.1, 123.0, 118.4, 108.3, 63.3, 57.9, 52.7, 46.0, 23.8, 14.9.; MS(EI$^+$): 191 (83%), 190 (100%), 162 (15%), 160 (16%), 148 (61%), 120 (28%), 104 (48%)
8. Prepared from 5-[6] and 6-hydroxy-1,2,3,4-tetrahydroisoquinolines[9], respectively. The N2 was acylated with methyl trifluoroacetate (1.2 eqv.) in DMF, and the phenolic hydroxy group was acetalized with 2,3-dihydro-4*H*-pyran (3 eqv.) in CH_2Cl_2 in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate. The trifluoroacetyl protection was finally removed with aqueous NaOH in dioxane. 5-Isomer: Yield 76 %. ^1H NMR ($CDCl_3$, 400 MHz): 7.07 (1H, t, 8.1 Hz), 6.92 (1H, d, 8.3 Hz), 6.66 (1H, d, 7.6 Hz), 5,43 (1H, t, 3.2 Hz), 3.99 (2H, s), 3.76 (1H, m), 3.61 (1H, m), 3.14 (2H, t, 6.1 Hz), 2.73 (2H, m), 1.5-2.1 (6H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.6, 137.2, 126.0, 124.3, 119.1, 111.2, 95.8, 61.9, 48.3, 43.7, 30.5, 25.2, 23.5, 18.9; MS (EI, 70 eV): 233 (M^+, 8 %), 148 (92 %), 132 (23 %), 120 (47 %), 91 (16 %), 85 (100 %). 6-Isomer: Yield 38 %. ^1H NMR ($CDCl_3$, 400 MHz): 6.92 (1H, d, 8.5 Hz), 6.84 (1H, dd, 8.3 Hz, 2.4 Hz), 6.80 (1H, d, 2.4 Hz), 5.38 (1H, t, 3.2 Hz), 3.92 (2H, s), 3.85-4.00 (1H, m), 3.55-3.67 (1H, m), 3.11 (2H, t, 6.1 Hz), 2.76 (2H, t, 5.9 Hz), 1.5-2.1 (6H,m); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.2, 135.9, 129.2, 127.1, 116.8, 114.5, 96.4, 62.0, 47.8, 43.8, 30.4, 29.5, 25.3, 18.8
9. Sall, D.J.; Grunewald, G.L. *J. Med. Chem.* **1987**, 30, 2208.
10. Tsunoda, T.; Yamamia, Y.; Ito, S. *Tetrahedron Lett.* **1993**, 34, 1639.
11. **3b** (15 mg) was placed in a small polypropylene column attached to two 2 mL syringes, one of which contained the tributylphosphine solution (0.1 mmol in 1 mL of THF) and the other one the appropriate alcohol (1 mmol in THF). The solution was flushed several times through the column, and then withdrawn into one of the syringes. The other syringe was used to add 1,1'-(azodicarbonyl)dipiperidine (0.1 μmol in 0.6 mL THF). The reaction mixture was left to stand 4 h at rt with occasional flushing. The solution was removed from the column, and the resin was washed with CH_2Cl_2 and MeOH (3 × 3 mL each), and dried under reduced pressure.
12. Prepared from from 5-[6] and 6-hydroxy-1,2,3,4-tetrahydroisoquinolines[9] essentially as described in *Ref.* 5. All compounds (**5a-m**) were identified by ^1H and ^{13}C NMR spectroscopy and EI mass spectroscopy.

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