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Fluorous scavenger for parallel preparation of tertiary sulfonamides leading to secondary amines

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Abstract—Alkylation of secondary sulfonamides by alkyl halides or alcohols (Mitsunobu reaction) is an efficient method for secondary amines preparation. However, its application to parallel chemistry is often difficult due to partial reaction. In this Letter, we propose a fluorous technique to bypass this problem. Thus, *o*-nitrobenzenesulfonamides were prepared and alkylated in parallel (Fukuyama method) with various alkyl halides or alcohols. Depending on the nature of the alkyl halide or alcohol, this step remained incomplete. A reactive fluorous alkyl iodide was then used to trap the unreacted sulfonamide allowing for a rapid and efficient fluorous solid-phase extraction (FSPE). Some examples of the isolated tertiary sulfonamides were converted in parallel to the corresponding secondary amines with good purity.

The parallel obtaining of pure secondary amines from primary amines remains a problematic purpose in organic synthesis.[1] Reductive aminations or direct alkylations of primary amines by alkyl halides may lead to mixtures of unreacted primary amines, secondary and tertiary amines whose separation remains difficult. A solution to this problem can be provided by the use of *ortho*- and/or *para*-nitrobenzenesulfonamides (nosyl groups, Fukuyama method,[2]) whose alkylation is possible by alkyl halides or under Mitsunobu conditions.[3] The compounds can be isolated as tertiary sulfonamides and their nosyl part is quantitatively removed to lead under mild conditions to secondary amines.[4,5] In spite of this advantage, incomplete alkylations may occur and limit the use of this method to activated agents in parallel syntheses. In response to this limitation, we propose here a rapid and efficient parallel method (Scheme 1) using a fluorous scavenger of the unreacted nosylsulfonamide portion allowing for the parallel isolation of pure tertiary sulfamides leading to secondary amines.

Our first attempts started with benzylamine **1** that was converted to the corresponding 2-nitrobenzenesulfonamide[4] **4** (90%). We have carried on many alkylation examples of nosylsulfonamide **4** with various alkyl halides, using classical conditions of the Fukuyama method (1.1 equiv of R^2X, 2.2 equiv of K_2CO_3, 60 °C, 20 h, DMF).[5] Some of these attempts resulted in complete reactions for activated R^2X such as allyl bromide and benzyl chloride or sterically unhindered alkyl halides (1-bromo or 1-iodobutane). However, under the same conditions, many alkylations of nosylamide **4** remained partial even with excessive R^2X and increase of the experiment duration. If this drawback is not an obstacle for individualized compound preparation, it requires a purification that clearly hinders its use in parallel synthesis. In response to this problem, we decided to trap the unreacted sulfonamide with a fluorous alkyl iodide[6] (Scheme 2).

The alkylation was initially attempted with $C_8F_{17}CH_2CH_2I$ (1.1 equiv, 20 h) but revealed incomplete. The use of $C_8F_{17}CH_2CH_2CH_2I$ (1.1 equiv added to the mixture of sulfonamide, R^2X and K_2CO_3 in excess in DMF) was necessary to obtain a total alkylation of the remaining starting material.[7] The resulting fluorinated nosylsulfonamide was then easily removed from the reactional mixture by the use of a fluorous solid-phase extraction leading to the isolated compound **4a**–**f**. This method was applied to other sulfonamides (nosylated aniline[4] **5** and nosylated tryptamine[8] **6**) and revealed comparable results (Table 1). Even if the yields appear variable, the purity, checked by TLC and HPLC, did

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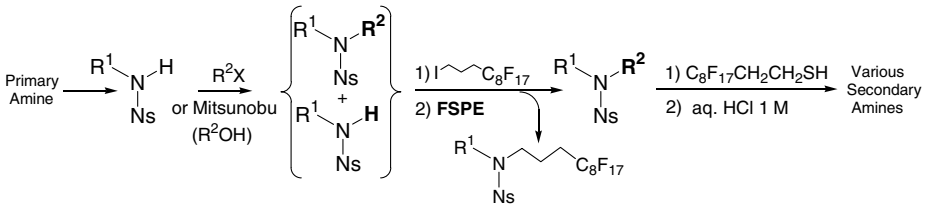
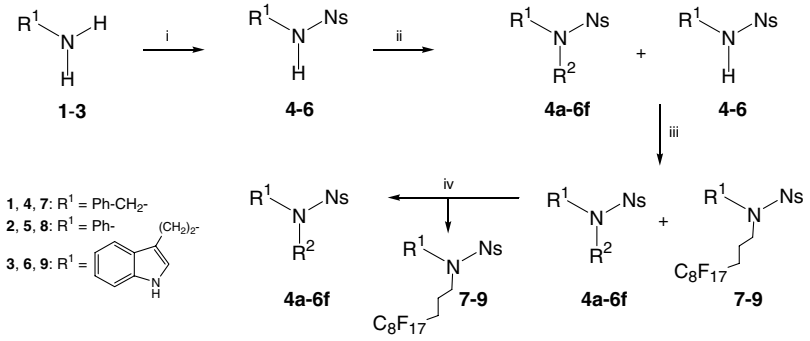


Scheme 1.



Scheme 2. Reagents and conditions: (i) 2-nitrobenzenesulfonyl chloride (NsCl, 1.2 equiv), Et_3N (1.2 equiv), CH_2Cl_2, rt, 2 h; (ii) R^2X (1.1 equiv, **a**: chlorobutane, **b**: 2-bromobutane, **c**: bromocyclopropane, **d**: bromocyclopentane, **e**: 2-bromopropane, **f**: 2-iodoethanol), K_2CO_3 (2.2 equiv), DMF, 60 °C, 20 h; (iii) $C_8F_{17}CH_2CH_2CH_2I$ (1.1 equiv), DMF, 60 °C, 20 h; (iv) FSPE (MeOH/H_2O: 8/2).

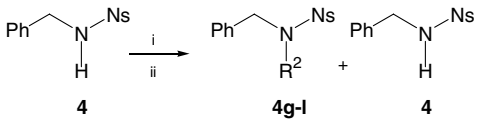
Table 1. Yields (%) of the various sulfonamides obtained by alkylation and Mitsunobu reaction

R^2X	**4a-f**	**5a-f**	**6a-f**	R^2OH	**4g-l**
	Yield (%)				Yield (%)
a Cl	44	79	73	**g** CH_3—(CH_2)—OH	59
b Br	82	72	66	**h** CH_3—OH	65
c Br	37	46	60	**i** OH	47
d Br	76	81	59	**j** OH, S	47
e Br	82	60	59	**k** OH	18
f HO, I	96	85	84	**l** O, O, OH	51

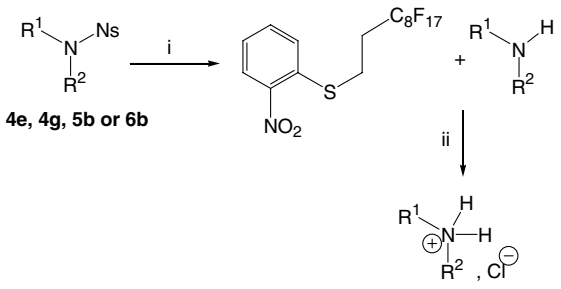
not reveal the presence of impurities. This result was conforted by ^1H and ^{13}C NMR. Only the examples **4e**, **5a** and **5c** showed the presence of small amounts of fluorinated sulfonamide in HPLC.

The feasibility of a comparable parallel method was then studied in the case of Mitsunobu reaction applied to nosylsulfonamide **4**. The procedure chosen was described by Pelletier and Kincaid[9] and used 1.2 equiv of an alcohol, supported triphenylphosphine (1.5 equiv), di-*tert*-butylazo-1,2-dicarboxylate (DBAD, 1.5 equiv) in CH_2Cl_2 for 20 h.[7] The parallel elimination of DBAD and the supported triphenylphosphine by appropriate treatment furnished a mixture of starting material (nosylsulfonamide **4** in our work) and its alkylated analogue **4g–l** (Scheme 3). Its treatment, previously described in Scheme 1 (1.1 equiv of $C_8F_{17}CH_2CH_2CH_2I$ and K_2CO_3 in DMF for 20 h at 60 °C), showed that trapping of the starting material and its easy elimination led to the pure sulfonamides **4g–l** (Table 1). The purity of the desired compounds was checked as presented for compounds **4a–f** and showed very satisfactory results.

The parallel removal of the sulfonamide moiety giving access to secondary amines was realized according to a procedure previously described by Christensen et al.[10] Some examples of our tertiary sulfonamides[11]



Scheme 3. Reagents and conditions: (i) R^2OH [1.2 equiv, **g**: octan-1-ol, **h**: methanol, **i**: propan-2-ol, **j**: 2-(3-thienyl)-ethanol, **k**: 2-(2-naphtyl)-ethanol, **l**: diethyleneglycolmonomethylether], triphenylphosphine polystyrene (1.5 equiv), DBAD (1.5 equiv), CH_2Cl_2, rt, 20 h; (ii) TFA/CH_2Cl_2: 1/1, rt, 1 h.



Scheme 4. Reagents and conditions: (i) $C_8F_{17}CH_2CH_2SH$ (2.5 equiv), Cs_2CO_3 (5 equiv), Et_2O, rt, 2 h; (ii) aq. HCl (1 M) extraction.

(compounds **4e**, **4g**, **5b** and **6b**) were individually reacted with a perfluorinated thiol in diethyl ether and led to perfluorinated 2-nitrobenzenethioether and to the corresponding secondary amines (Scheme 4). The latter were extracted with aqueous hydrochloric acid and furnished the desired ammonium salts in an average yield of 70% and in good purity (>90%, controlled through TLC, HPLC, ^1H and ^{13}C NMR).

In conclusion, this procedure aiming to trap the unreacted portion of starting material is suitable for parallel alkylation of sulfonamides with diverse alcohols and alkyl halides especially if these latter were little reactive. Indeed, secondary amines were easily obtained in variable yields but always with good purity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.110.

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7. *General procedure for synthesis and purification of tertiary sulfonamides:* (a) *From alkyl halides R^2X:* Secondary sulfonamide **4**, **5** or **6** (1 equiv), K_2CO_3 (2.2 equiv), alkyl halide (1.1 equiv) and DMF (1 mL) were stirred at 60 °C for 20 h. The iodide $C_8F_{17}CH_2CH_2CH_2I$ (1.1 equiv) was added and the mixture was stirred at 60 °C for 20 h. After filtration of the K_2CO_3, the solution was concentrated under reduced pressure and purified by FSPE. The identity and purity of the compounds were evaluated by TLC, HPLC, ^1H and ^{13}C NMR. (b) *From alcohols R^2OH*: Secondary sulfonamide **4** (1 equiv), alcohol (1.2 equiv) and triphenylphosphine polystyrene (1.5 equiv) were placed in CH_2Cl_2. The DBAD (1.5 equiv) in CH_2Cl_2 was added and the mixture was stirred at room temperature for 20 h. Then, TFA was added and the stirring was maintained for 1 h. After filtration of the resin, the mixture was concentrated under reduced pressure and the residue was dissolved in DMF (1 mL). K_2CO_3 (1.1 equiv) and $C_8F_{17}CH_2CH_2CH_2I$ (1.1 equiv) were added and the solution was stirred again at 60 °C for 20 h. After removal of the K_2CO_3, the mixture was concentrated under reduced pressure to obtain a mixture of secondary and the tertiary sulfonamide. The pure tertiary sulfonamide was purified by FSPE. The identity and purity of the compounds were evaluated by TLC, HPLC, ^1H and ^{13}C NMR. (c) *FSPE*: The residue was then loaded onto a 5 g fluorous silica gel cartridge (Silica gel 60 C8-reversed phase perfluorinated 35–70 μm, Fluka) which had been preconditioned in methanol. The non-fluorous tertiary sulfonamides were first eluted with 3×10 mL of MeOH/H_2O (80/20). Subsequent wash with 4×10 mL of diethyl ether allowed the fluorous tertiary sulfonamides to be eluted. The MeOH/H_2O fractions were combined and concentrated under reduced pressure. After washing with 10 mL of methanol, the fluorous silica gel cartridge could be reused.
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11. *General procedure for conversion of tertiary sulfonamides into secondary amines*: A mixture of a tertiary sulfonamide (1 equiv), Cs_2CO_3 (5 equiv), $C_8F_{17}CH_2CH_2SH$ (2.5 equiv), in Et_2O was stirred at room temperature for 2 h. After elimination of the Cs_2CO_3 by filtration, the organic layer was extracted with 1 M aqueous HCl and concentrated under reduced pressure to obtain the final amine as its hydrochloride salt.