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Solid phase deprotection of 2-nitrobenzenesulfonamides: synthesis of simple 2-(alkylamino)-pyrroles

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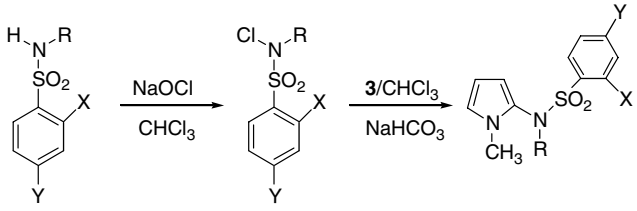
Abstract—The 2-nitrobenzenesulfonamide cleavage using a solid-phase thiophenolate reagent gives simple 2-(alkylamino)-pyrroles without the presence of the competing nucleophilic substitution product.

No general method exists for the preparation of simple 2-(alkylamino)-pyrroles without further substitution on the pyrrole ring.[1] Only a few scattered references to their preparation are known. Recently routes to more highly substituted derivatives have appeared.[2,3] We have shown that it is possible to obtain previously unknown simple 2-aminopyrrole derivatives by removing the imide group from *N*-(1-substituted-1*H*-pyrrol-2-yl)phthalimide derivatives.[4] An analogous strategy using 2-nitrobenzenesulfonamide derivatives can be used to prepare simple 2-(alkylamino)-pyrroles.

Fukuyama and co-workers reported that the 2-nitro- and 4-nitrobenzenesulfonamide groups can be removed with either thioacetic acid or thiophenol in LiOH/DMF to give amine derivatives.[5,6] Previously we reported that 1-methylpyrrole (**3**) reacts with *N*-chloro-*N*-(4-substituted-phenyl)benzene sulfonamides to give a pyrrole derivative in which the benzenesulfonamide group was incorporated at C2 of the pyrrole ring.[7] Removal of the benzenesulfonamide group using the Fukuyama method would give a 2-aminopyrrole derivative.

To this end a model benzenesulfonamide derivative **4a** (X = H, Y = NO_2 and R = 2-propyl) was prepared as indicated in the scheme below. The structure of **4** was confirmed by NMR and exact mass spectroscopy.[8] Yields of **4** appeared to be influenced by the steric bulk of R. It should be noted that the NMR spectra of derivatives **4a**–**c** indicated the possibility of restricted rotation.[9] For example, in the case of the 2-propyl derivative **4a**, two non-equivalent methyl groups were observed by proton NMR.



1a (R=2-propyl)	**2a** 97%	**4a** 19%
1b (R=*n*-propyl)	**2b** 98%	**4b** 63%
1c (R=*n*-butyl)	**2c** 96%	**4c** 38%
1d (R=*t*-butyl)	**2d** 86%	**4d** 15%

The benzenesulfonamide group was successfully removed with thiophenol/LiOH/DMF but not with thioacetic acid/LiOH/DMF. Proton NMR spectra of reaction mixtures indicated that conversion was not complete (benzenesulfonamide moiety still present). Yields of **5a** were not affected by either increasing the reaction time or the amounts of thiophenol and LiOH relative to the benzenesulfonamide **4a**. The desired product was unstable and decomposed during attempts to

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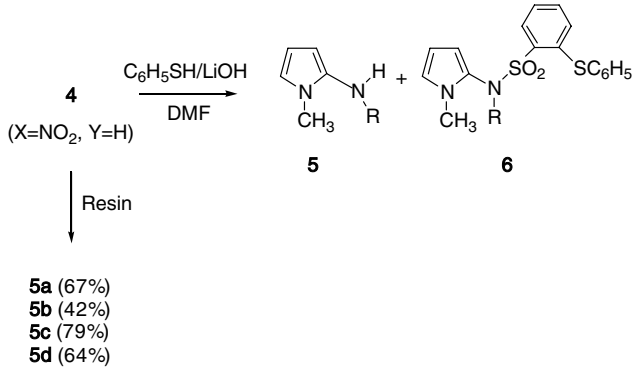
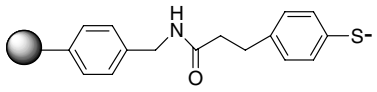
isolate it by column chromatography. Simple 2-aminopyrroles have been isolated as their tetraphenylborate salts but the analogous salt of **5a** was unstable.[4]

Wuts and Northuis reported that during the thiolate cleavage of a 4-nitrobenzenesulfonamide derivative nucleophilic displacement of the nitro group was also observed.[10] This was not observed when a 2-nitro derivative was used. It was proposed that the effect was steric in nature. This suggested that nucleophilic substitution of the 4-nitro group by the thiophenolate group to give the *para* isomer of **6** was competing with the desired sulfonamide cleavage to give **5a**. Based on this, the synthesis of **5** was attempted with the 2-nitrobenzenesulfonamide derivative **4a** (X = NO_2, Y = H and R = 2-propyl) but nucleophilic displacement of the nitro group (30%) was still observed as a side reaction. An attempt was made to prepare the analogous 2,4-dinitrosulfonamide derivative of **4** [X = Y = NO_2 and R = 2-propyl], but cleavage of the 2-propyl group occurred during the N-chlorination step.[11] The 4-fluorobenzenesulfonamide (X = H, Y = F and R = 2-propyl) and 2,4-difluorobenzenesulfonamide (X = Y = F and R = 2-propyl) derivatives of **4** were prepared. Nucleophilic substitution of the fluoro group was also observed. And in the case of the 4-fluorobenzenesulfonamide derivative, nucleophilic displacement of the fluoro group was the only reaction observed. Proton NMR confirmed the structure of the *para* isomer of **6**.[12] Cleavage was attempted using 2,6-dimethylthiophenol/LiOH but even with this hindered thiophenolate nucleophilic substitution successfully competed with benzenesulfonamide cleavage.



Given these results a solid-phase method was developed for carrying out the cleavage of the 2-nitrobenzenesulfonamide group in **4a** (R = 2-propyl). It would be expected that if the thiophenolate group was attached to a solid support the nucleophilic substitution product analogous to **6** would remain bound to the resin. Filtration of the reaction mixture would then give pure product. Synthesis of pure **5a**, in solution, has been realized using a commercial resin containing a protected thiophenol group that, when unmasked, generates the thiophenolate group shown below.[13] This method can be compared to a recent study that used a perfluorinated thiol for deprotection followed by solid phase extraction to give the amine.[14]



thiophenolate resin

The 2-nitrobenzenesulfonamide derivative **4a** (0.08 mmol, ca. 25 mg) was combined with two equivalents of the treated resin in 1.0 mL of DMF-d_7, the stirred mixture was heated for 12 h at 100 °C under argon and the resin removed by filtration. Proton NMR of the DMF-d_7 solution indicated that the only product present in solution was the 2-(alkylamino)-pyrrole **5a**.[15] Similar results were obtained for the other 2-(alkylamino)-pyrroles **5b–d**. Yields were obtained by proton NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard.

Given the large number of possible benzenesulfonamide derivatives possible this method is a general route to 2-(alkylamino)-pyrroles. The solid-phase method described here is an alternative to the solution reaction developed by Fukuyama and co-workers. Its use would be appropriate in situations where nucleophilic substitution of the nitro group is problematic or where the use of a volatile thiol is to be avoided.

Acknowledgements

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8. Compound **4a** (R = 2-propyl): ^{1}H NMR (300 MHz, CDCl3): δ 7.84–7.56 (m, 4H), 6.65 (br, 1H), 6.07 (br, 1H), 5.78 (br, 1H), 4.72–4.53 (m, 1H), 3.47 (s, 3H), 1.09 (t, 6H); HRMS (M+H) expected 324.1018, experimental 324.1012.
9. This will be the subject of a separate publication.
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12. Compound **6** (R = 2-propyl, *para* isomer): ^{1}H NMR (300 MHz, C_2D_7NO): δ 7.91–7.05 (m, 9H), 6.64 (br,

1H), 6.01 (br, 1H), 5.60 (br, 1H), 4.60–4.38 (m, 1H), 3.58 (s, 3H), 1.02 (d, J = 3.7 Hz, 3H), 0.85 (d, J = 5.5 Hz, 3H).

13. Novabiochem's 3-(4-(tritylmercapto)phenyl)propionyl AM resin 100–200 mesh and 0.88 mmol/g was activated according to the manufacturer's instructions.
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15. Compound **5a**: ^{1}H NMR (300 MHz, C_2D_7NO): δ 8.34–8.25 (m, 1H), 7.94–7.86 (m, 1H), 7.79–7.70 (m, 1H), 1.35 (d, J = 5.5 Hz, 6H); peaks for N–CH_3 and isopropyl CH are covered by signal for water.