SYNTHESES WITH STABLE ISOTOPES: 4-ETHYLSULFONYL-1-NAPHTHALENESULFONAMIDE-^{15}N

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SUMMARY

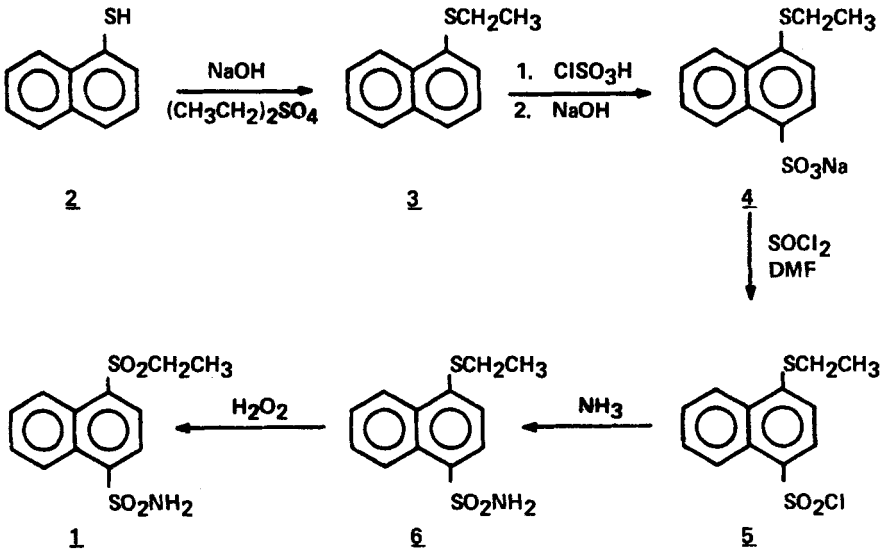
The title compound was prepared from 4-ethylthio-1-naphthalenesulfonyl chloride in a two-step synthesis with an overall yield of 56%. An alternative one-step synthesis from 4-ethylsulfonyl-1-naphthalenesulfonyl chloride was found to be unsuitable for nitrogen labeling.

Key Words: 4-ethylsulfonyl-1-naphthalenesulfonamide-^{15}N, nitrogen-15.

INTRODUCTION

4-Ethylsulfonyl-1-naphthalenesulfonamide (1, ENS) has been reported (1) to promote experimental bladder carcinogenesis. ENS was first synthesized by Brimelow and Vasey (2) from 4-amino-1-naphthalenesulfonic acid. Brimelow and Vasey did not report yields for their synthesis, but Turner and Dean (3) have stated that the method of Brimelow and Vasey gives low yields. Turner and Dean have described their own synthesis of ENS starting with 4-nitro-1-naphthylamine and utilized their method for labeling the sulfonamide sulfur of ENS with sulfur-35. Our interest in labeling ENS with nitrogen-15 prompted us to investigate the applicability of Turner and Dean's method which introduces both sulfur functions by diazonium salt reactions. In our hands, the best overall yields of ENS from 4-nitro-1-naphthylamine were on the order of 10%, and, as discussed later, the last step of the reaction is not well suited to nitrogen labeling. We have recently reported (4) a new, convenient, five-step synthesis of ENS from

1-naphthalenethiol (2) which avoids diazonium salt reactions. The reaction sequence, which is shown in Scheme 1, gives ENS in an overall yield of 50-60%. In this paper, we wish to report the preparation of ENS labeled with nitrogen-15 by this method.

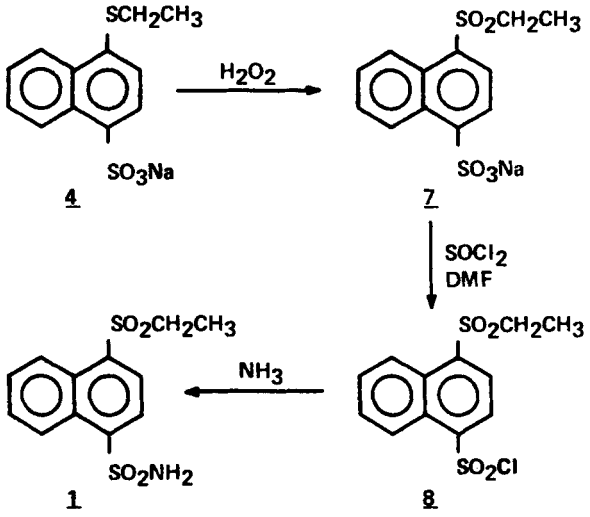


Scheme 1

DISCUSSION

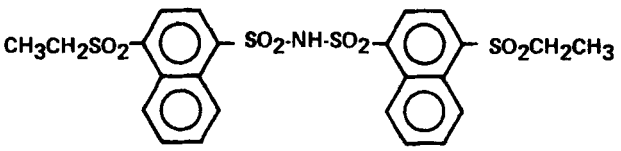
Preparation of the acid chloride 5 from 1-naphthalenethiol (2) has been described (4) and can be conveniently accomplished in 70-75% overall yield for the three steps shown in Scheme 1. Our previous work (4) utilized excess ammonia for the conversion of 5 to 6 and, since these conditions are not desirable for nitrogen labeling, we sought to find suitable conditions for the conversion of 5 to 6 using ammonium sulfate as a source of ammonia. After experimenting with a variety of solvent systems and bases for *in situ* generation of ammonia from ammonium sulfate, we found the most suitable conditions to be potassium carbonate and aqueous acetonitrile which gave 6 in 85% yield.

An alternative synthetic approach to ENS in which the order of functional group transformations is altered is shown in Scheme 2. Thus, the thioether 4 was converted to the sulfone 7 in 80% yield by hydrogen peroxide in aqueous acetic acid, and the sodium sulfonate group of 7 was transformed to a sulfonyl chloride



Scheme 2

function by the method of Bosshard, et al. (5) to give 8 in 80% yield. These procedures were similar to those described (4) for the conversion of 6 to 1 and 4 to 5. Compound 8 was prepared, but not isolated, by Turner and Dean (3) and converted into ENS by treatment with excess aqueous ammonia. We found that the acid chloride 8, when dissolved in acetonitrile and treated with excess ammonia gas, was smoothly converted to ENS in 98% yield. However, when the same transformation was attempted using the aqueous acetonitrile-ammonium sulfate-potassium carbonate system, the yield of ENS was only 33%. Thin-layer chromatography (silica gel, ethyl acetate) of this reaction mixture showed a fluorescent spot at R_f = 0.8 (ENS) and a second fluorescent component at R_f = 0.2. The R_f = 0.2 compound was also observed when the potassium salt of ENS (prepared from ENS and aqueous potassium carbonate) was allowed to react with the acid chloride 8. We suggest that the R_f = 0.2 compound has the sulfonimide structure shown below and



is formed by the reaction of the ENS anion with the acid chloride 8 when ammonia is not present in excess. Since an ethylsulfonyl group is a stronger electron withdrawing group than the ethylthio group, it is not surprising that the

reaction of the acid chloride 8 with limited ammonia (in the presence of potassium carbonate) is accompanied by the sulfonimide side reaction, while the analogous reaction of the acid chloride 5 is not. In summary, both reaction scheme 1 and reaction scheme 2 are suitable for preparing ENS itself, but only reaction scheme 1 is suitable for preparing ENS from limited amounts of ammonia generated in situ.

EXPERIMENTAL

Materials and Methods--Melting points were determined using a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710 spectrophotometer using polystyrene calibration lines and are reported to the nearest 10 cm^{-1} with natural abundance absorptions given in parentheses. Ammonium-^{15}N sulfate (98.5% ^{15}N) was produced at this Laboratory.* Reactions were monitored and product purity was checked by thin-layer chromatography on precoated silica gel 60 F-254 plates (EM Laboratories) using toluene-ethyl acetate (1:1, v/v) as a developing solvent. The approximate R_f values of the compounds were: 5 (0.91), 6 (0.64), 1 (0.47). Silica gel 60 (0.063-0.2 mm, EM Laboratories) was used for column chromatography.

4-Ethylthio-1-naphthalenesulfonamide-^{15}N--An Erlenmeyer flask was charged with 4-ethylthio-1-naphthalenesulfonyl chloride (4) (5.16 g, 18 mmol), ammonium-^{15}N sulfate (1.21 g, 9 mmol), potassium carbonate (9.94 g, 72 mmol), and acetonitrile (72 ml). After cooling in an ice bath, water (36 ml) was added, and the flask was securely stoppered. After stirring for a few minutes, the ice bath was removed, and the two-phase mixture was magnetically stirred at room temperature for 1.5 hr. The layers were separated and the aqueous layer was discarded, since it gave no precipitate upon acidification. After removing the solvent from the organic layer, the residue was acidified with 5% hydrochloric acid to give the crude product which was filtered, washed with water, and dried to give a pale-yellow solid (4.61 g), mp 139-142°.

Approximately one-half of the crude product was dissolved in ethyl acetate and chromatographed through a silica gel column (2.4 x 30 cm), eluting with ethyl

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acetate. After chromatographing the second half of the crude product in a similar manner, the fractions containing the product were combined, and the solvent was evaporated to give 3.32 g (69%) of 4-ethylthio-1-naphthalenesulfonamide-^{15}N as a colorless solid. Ir (KBr): 3350 (3370), 3260 (3270), 1540 (1560), 1500, 1310 (1330), 1210, 1160, 1140, 910, 760, 680 cm^{-1}.

4-Ethylsulfonyl-1-naphthalenesulfonamide-^{15}N--A mixture of 4-ethylthio-1-naphthalenesulfonamide-^{15}N (3.32 g, 12.4 mmol), acetic acid (19 ml), and 30% hydrogen peroxide (9.5 ml, ca. 90 mmol) was heated on a steam bath for 1.5 hr. The resulting solution was diluted with water (125 ml) and cooled in an ice bath. The product which separated was filtered, washed with water, and dried to give 3 g (81%) of pale-yellow needles, mp 198-199° (decomp.). The product was recrystallized from ethanol (Norit) to give 2.5 g of colorless plates, mp 199-200° [reported (2,3), 198°]. Ir (KBr): 3330 (3350), 3250, 3110, 2970, 2920, 1560, 1500, 1450, 1340, 1310, 1280, 1190, 1170, 1150, 1130, 1040, 980, 910, 760, 720, 670 cm^{-1}.

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