FACILE SYNTHESIS OF N-SUBSTITUTED 1H-AZEPINE DERIVATIVES[1]

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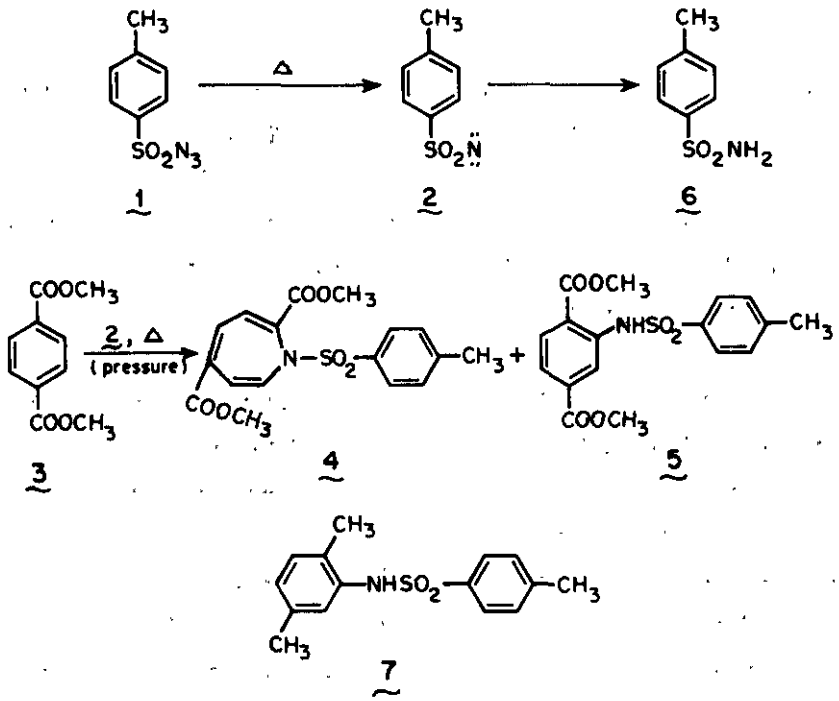
Abstract - The facile synthesis of N-sulphonyl and N-ethoxycarbonyl substituted 1H-azepines in high yields by the pressure-induced sulphonylnitrene insertion reaction or, in anhydrous solvents, the 1,3-dipolar azide addition reaction with aromatic substrates containing electron-withdrawing substituents (e.g. dimethyl terephthalate) are described. The probable sequences of reactions involved in the two cases have been indicated.

Recently we reported the synthesis of N-(p-toluenesulphonyl)-1H-azepine by the thermal decomposition of p-toluenesulphonylazide (Tosylazide) 1 in excess of benzene under positive nitrogen pressure.[2] By judicious choice of reaction temperature and pressure, the yield of the azepine formed was optimised.

In the present communication, we have shown that the method can be used with advantage for the synthesis of N-sulphonylazepine derivatives by the insertion of sulphonylnitrenes in aromatic systems containing electron-withdrawing substituents. The formation of N-(p-toluenesulphonyl)-2,5-dimethoxycarbonyl-1H-azepine 4 in 15% yield by the thermolysis of 1 in dimethyl terephthalate (DMT) 3 at 155-160°C and atmospheric pressure was described from this laboratory;[3] and plausible course of the reactions involved in the formation of sulphonylazepines, having electron-withdrawing substituents on carbon atoms adjacent to the ring nitrogen was suggested.[4] Evidence is in favour of the initial formation of the sulphonylnitrene 2 and its involvement in further reactions with aromatic substrates such as 3 to give ultimately the azepine and anilide. The reactive nitrene 2 is also responsible for the formation of hydrogen abstraction product 6.

Now we have found that the yield of the azepine derivative 4 can be considerably increased by carrying out the thermolysis of 1 in molten 3 under nitrogen pressure. In a typical experiment, the liquid tosylazide 1 (7.0 g) and DMT 3 (600 g) were placed in a high pressure reactor (S.S. Autoclave Engineers, Inc., U.S.A.), which was earlier purged with nitrogen.

The temperature was gradually raised to 155°C during 0.5 h, with simultaneous adjustment of the nitrogen pressure in the reactor to 60-62 atm. The mixture was stirred at 155-160°C under this pressure for 2.5 h and cooled. The excess of unreacted DMT was removed by dissolving the solid reaction mass in benzene: pet.ether (7:3) mixture and allowing to crystallize. Bulk of the crystallized DMT was removed by filtration and washed with benzene: pet.ether mixture. The filtrate and washings were collected. The DMT was repeatedly dissolved in the same solvent mixture and recrystallised five times. Finally, pure DMT (checked by



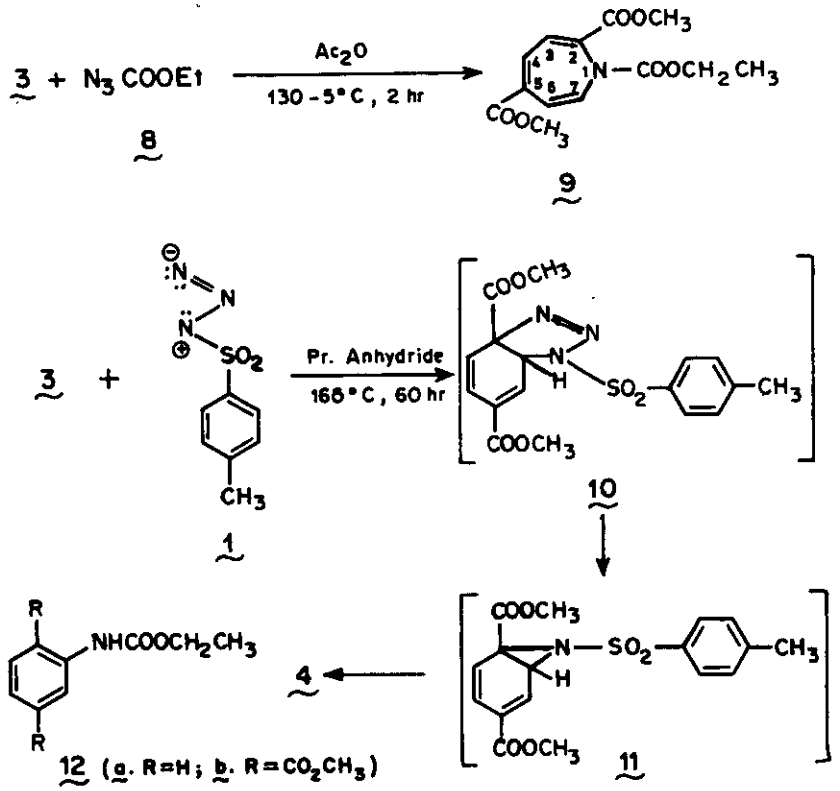
t.l.c.) was removed from the reaction mixture. The combined filtrates and washings contained only traces of DMT, and, on concentration, yielded crystalline yellow coloured azepine 4 (7.0 g). It was collected by filtration and the filtrate was evaporated to dryness. The resulting residue was dissolved in minimum amount of acetone, adsorbed on silica gel and subjected to chromatographic separation. Elution with pet.ether gave traces of DMT as the first fraction. The second fraction, which was obtained by eluting with benzene: pet.ether (1:1) gave more of the azepine 4 (0.6 g). The combined azepine (7.6 g) on further crystallization from benzene: pet.ether (1:1) gave pure 4 (7.5 g, 70.6%), mp 127°C (lit.[3] mp 126°C, mixed mp

undepressed). From the other fractions, N-(p-toluenesulphonyl)-2,5-dimethoxycarbonylanilide 5 (0.2 g, 1.88%), mp 148°C (lit.[3] mp 148°C) and toluene-p-sulphonamide 6 (0.27 g, 4.5%), mp 137°C (lit.[2] mp 136°C) were obtained. Pure DMT 2 (590 g) was also recovered. The structure of 4 was confirmed from its direct comparison with an authentic sample[3] and spectro-analytical data [pmr ($CDCl_3$): δ 2.4 (3H, s, aryl-CH_3), 3.7 (3H, s, 5-$COOCH_3$, 3.8 (3H, s, 2-$COOCH_3$), 6-7.6 (8H, m, aryl and azepine ring H) ppm. ir ($CHCl_3$): 3030, 2960, 1720, 1620, 1590, 1430, 1370, 1280 and 1170 cm^{-1}]. It is clear that the positive high pressure during the reaction resulted in more than four-fold increase in the yield of the azepine.

Thermolysis of sulphonylazides in aromatic systems containing electron-donating groups did not result in the formation of azepine derivatives. Even high pressure thermolysis in such cases resulted in only the sulphonanilides. Thus the thermolysis of 1 (16.0 g) in p-xylene (1050 ml) at 155-160°C and 74-75 atm pressure for 2 h and working up the reaction mixture by subjecting to chromatographic separation on silica gel using pet.ether and benzene and recrystallization from ethanol gave colourless crystals of N-(p-toluenesulphonyl)-2,5-xylidide 7 (5.4 g, 24.2%), mp 120°C (lit.[3], mp 120°C). Small amount of p-toluenesulphonamide, 6 (0.23 g) was also isolated. There was no evidence of the presence of any azepine derivative in the reaction mixture.

An attempt to react ethyl azidoformate 8 (2.0 g) with DMT 3 (20 g) at 155-160°C and atmospheric pressure resulted in an explosive reaction with visible flame. In order to conduct smooth thermal reaction of 8 with DMT 3, we looked for a suitable solvent medium, which would provide the critical reaction temperature without participating in the reaction. Since it was known that ethyl azidoformate 8 reacts[5] at about 125-130°C and tosylazide 1 needs about 155-160°C for reaction, we chose respectively acetic anhydride (bp 138°C) and propionic anhydride (bp 167°C) as solvents for their thermal reactions. They did not react with the respective azides 8 and 1, even when refluxed for 6 h. When ethyl azidoformate 8 (4.0 g) was added gradually at 125-130°C to a solution of DMT 3 (40.0 g) in acetic anhydride (100 ml) and refluxed for 2 h, the hitherto unknown 1-ethoxycarbonyl-2,5-dimethoxycarbonyl-1H-azepine 9 (yellow crystals from benzene), mp 94-95°C was isolated in 1% yield [pmr (CCl_4): δ 1.2 (3H, t, $COOCH_2CH_3$), 3.7 (6H, s, $COOCH_3$ -2,5), 4.3 (2H, q, $COOCH_2CH_3$), 6.0 (2H, d, 3,6-H), 6.7 (1H, m, 4-H), 7.2 (1H, m, 7-H) ppm. ir (nujol) : 1701, 1640, 1587, 1450, 1380, 1316 and 1266 cm^{-1}. m/e, 281 (M^+, 100%)]. The fragmentation pattern in the mass spectrum of 9 was consistant with its structure.

The thermal reaction of 1 (2.0 g) with DMT 3 (20 g) at 165°C in refluxing propionic anhydride (100 ml) was carried out for a prolonged period of 60 h. The solvent was removed under reduced pressure and the excess of 3 was removed as before by crystallization from benzene: pet. ether mixture. The filtrate and washings, free from DMT were concentrated and the dissolved products adsorbed on silica gel for chromatographic separation. Elution with pet.ether gave unreacted azide 1 (1.1 g, 55%). The second fraction gave traces of DMT; and the last one yielded the desired pale yellow crystalline azepine 4, mp 127°C (mixed mp undepressed) in 40% yield (1.2 g). The anilide 5 and the sulphonamide 6 were conspicuously absent. Formation of only the azepine 4, which is the ring expansion product, absence of the direct insertion product such as the anilide 5 and the typical hydrogen abstraction product, the sulphonamide 6, and the recovery of unreacted tosylazide 1, suggest that under the reaction conditions in the anhydrous solvents, the initial attack of the azide 1 on the aromatic substrate 3 involves the 1,3-dipolar addition in a concerted fashion. The simultaneous two C-bond formations lead to the triazoline 10, which loses nitrogen to give the aziridine 11 and finally the azepine 4. Similar sequence of reactions is apparently involved in the reaction of 8 with 3 in acetic anhydride to give the azepine 9 as the sole product. A number of examples[6,7] in the literature support the formation of such intermediate triazolines. The sulphonylazide 1 is more specific in giving the comparatively more stable sulphonylazepine 4 than the ethyl azidoformate 8, which gave the N-ethoxycarbonylazepine 9 in much lesser yield. Of course, the latter reaction was carried out for much lesser duration. When this reaction was carried out in refluxing acetic anhydride for a longer duration of 6 h, only an oily liquid was isolated. It has been reported[8] that N-ethoxycarbonylazepine on heating gave ethyl N-phenyl-carbamate 12a. Presumably the azepine 9, formed initially has undergone similar thermal rearrangement on prolonged heating to give ethyl N- (2,5-dimethoxycarbonyl phenyl) carbamate 12b, as the main constituent of the oily liquid. [pmr (CCl_4): δ 1.4 (3H, t, C-CH_3), 3.5 (6H, two singlets very close to one another; two carbmethoxy groups), 4.4 (2H, q, -CH_2), 7.3-8.2 (3H, m, aromatic protons), 7.85 (1H, NH-proton, peak merged in aromatic region) ppm. ir (nujol): 3180, 1720, 1635, 1360, 1285, 1230, 1180 and 1115 cm^{-1}. m/e 281 (M^+)]. The fragmentation pattern in the mass spectrum of 12b was in agreement with its proposed structure.



All the compounds (except 12b) described in this communication were found to be single substances by t.l.c. and gave satisfactory elemental analyses.

The facile synthesis of N-sulphonylazepine rings via the pressure-induced nitrene insertion reaction or the 1,3-dipolar azide addition reaction with aromatic substrates containing electron-withdrawing substituents is interesting from the point of view of new biologically active compounds. The interest in the azepine ring system is because of its presence in a number of drug compounds.[9] The rhoeadine type alkaloids have benzazepine as the basic structure.[10] The sulphonylazepines described here and elsewhere[2,3,4] may exhibit promising biological activity, because of the presence of both the sulphone functional group and the azepine ring.

This communication is dedicated in humble tribute to Professor Herbert C. Brown on the occasion of his 70th birthday. One of the authors (NRA) had the privilege to be associated with him for two years (1961-63).

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