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On the Reaction of Anthranilic Acid with Thionyl Chloride: the Actual Structure of "Kametani's Sulfinamide Anhydride"

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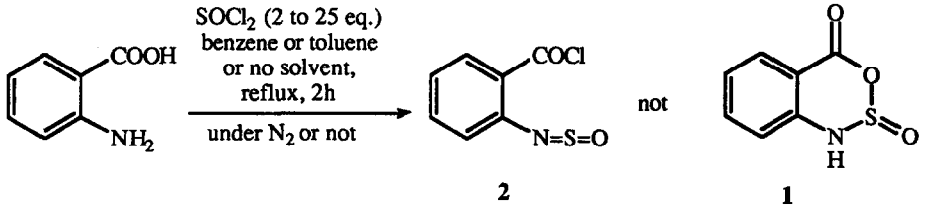
Key Words: anthranilic acid; iminoketene; thionyl chloride; sulfinylamines; Kametani's sulfinamide anhydride.

Abstract: *Despite previous reports, no sulfinamide anhydride is formed from the reaction of anthranilic acid with thionyl chloride, the actual product being 2-sulfinylaminobenzoyl chloride. This excludes iminoketene formation in the reactions of this activated form of anthranilic acid.*

In 1976 Kametani *et al.* introduced the retro mass spectral synthesis approach[1,2], which has found widespread use in organic and organometallic chemistry. This approach makes extensive use of hetero Diels-Alder reactions and was first exemplified by the synthesis of several quinazolinocarboline alkaloids, using as a synthon the iminoketene derived from anthranilic acid, a well-known species in mass spectrometry. The synthetic equivalent of that synthon was prepared[1] by the reaction of anthranilic acid with excess thionyl chloride in benzene, and identified by its ir and mass spectra as 3,2,1-benzoxathiazin-4(1H)-one-2-oxide **1**.

The extremely simple preparation of this activated form of anthranilic acid has led, since then, to the synthesis of many natural and unnatural compounds[3], taking advantage of its high reactivity towards imines, amides and amines. We repeated many of these reactions and were able to reproduce the preparative results.

Nevertheless, we wish to report that **1** is not formed from the reaction of anthranilic acid with thionyl chloride, the actual product being 2-sulfinylaminobenzoyl chloride **2**. We have carried out the reaction in widely different conditions (two-, five-[4], ten-[1], or twentyfivefold[5] molar excess of thionyl chloride, inert atmosphere or not, varying amounts of solvent) and the same surprising result is always obtained (Scheme).



2 **1**

Scheme

Compound **2** can be purified by distillation and its structure is fully supported by its ir and high-resolution mass spectra[6]. Moreover, a study of the literature revealed that our results were in perfect agreement with those of Graf[7] who, as early as 1937, studied the reactions of the three aminobenzoic acids with neat refluxing thionyl chloride. The discrepancy in assigning structure **1** or **2** had already been noted[8], but no further effort was made to elucidate it; only the unexpected behaviour of 5-nitroanthranilic acid was studied in detail.

We have also found that no sulfinamide anhydrides are formed when the reactions are carried out with some ring-substituted anthranilic acids, such as the 4,5-dimethoxy[9, 3f] and the 5-methyl[3f] derivatives, both of which were reported to do so. Again, the actual products are the corresponding 2-sulfinylaminobenzoyl chlorides.

Because of its formal resemblance with isatoic anhydride, we thought that **1**, if formed, could be easily opened by excess thionyl chloride, in the same way as isatoic anhydride is transformed into 2-isocyanatobenzoyl chloride. Nevertheless, when stoicheometric quantities of anthranilic acid and thionyl chloride were used, no **1** was detected, compound **2** being again formed, although in lower yield.

In conclusion, the useful chemistry of 2-sulfinylaminobenzoyl chloride **2** has been inadvertently developed in the last fifteen years, and not that of **1** which, to our knowledge, has not yet been prepared. This means that iminoketene cycloaddition mechanism, which has been demonstrated in some reactions of isatoic anhydride[10], can no longer be postulated to explain the reactivity of **2**.

REFERENCES AND NOTES

1. Kametani, T.; Higa, T.; Loc, C.V.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186-6188.
2. Kametani, T.; Fukumoto, K. *Acc. Chem. Res.* **1976**, *9*, 319-325.
3. See *inter alia*: (a) Kappe, T.; Stadlbauer, W. *Adv. Heterocyclic Chem.* **1981**, *28*, 127-182. (b) Hermecz, J.; Vasvári-Debreczy, L. *ibid.* **1986**, *39*, 281-385. (c) Kametani, T.; Hibino, S. *ibid.* **1987**, *42*, 245-333. (d) Bergman, J.; Bergman, S. *J. Org. Chem.* **1985**, *50*, 1246-1255. (e) Fodor, L.; Szabó, J.; Bernath, G.; Sohár, P. *Tetrahedron Lett.* **1984**, *25*, 2013-2016. (f) Jakobsen, M.H.; Buchardt, O.; Holm, A.; Meldal, M. *Synthesis* **1990**, 1008-1010.
4. Kametani, T.; Loc, C.V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306-2309
5. Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 1922-1926.
6. B.p. 110-112°C/0.7 Torr; m.p. 32-34°C; ir ($CHCl_3$) 1778, 1736(ν C=O), 1120 cm^{-1}; the strong absorption band observed in the neat spectrum at 1192 cm^{-1} can be attributed to the N=S=O group; ms (VG, AutoSpec) M^+ 200.9656 (calcd. for $C_7H_4ClNO_2S$, 200.9651); the (M - Cl) is the base peak of the spectrum; no ions detected at 183 or 119 Da.
7. Graf, R.; Langer, W. *J. Prakt. Chem.* **1937**, *148*, 161-169.
8. Tani, J.; Yamada, Y.; Oine, T.; Ochiai, T.; Ishida, R.; Inoue, I. *J. Med. Chem.* **1979**, *22*, 95-99.
9. Kametani, T.; Loc, C.V.; Higa, T.; Ihara, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. I* **1977**, 2347-2349.
10. Crabtree, H. E.; Smalley, R. K.; Suschitzky, H. *J. Chem. Soc. (C)* **1968**, 2730-2733.

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