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FORMATION OF HETEROCYCLIC RINGS

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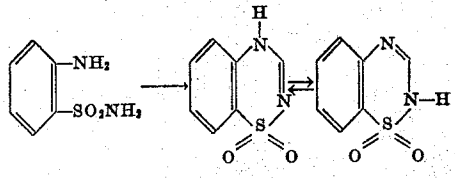
My invention relates to the production of 1,2,4-benzothiadiazine-1,1-dioxides, and particularly to a process which produces these compounds by a ring-closure method which may be represented as follows:



The benzenoid nucleus may carry one or more substituents in addition to the amino and sulfamyl radicals which are shown. Such other radicals may be another amino or sulfamyl group, halogen, lower alkyl which may or may not be substituted with halogens, hydroxy or alkoxy or nitro radicals. Representative of such substituted benzenoid starting materials are the ones described and claimed in Novello Patent 2,809,194.

The aforementioned patent proposes effecting the desired ring closure by the use of large amounts of formic acid. While this mode of preparation is in many respects highly satisfactory, it has the disadvantage that a very large molar excess of formic acid must be used. Another method proposes to use formamide to effect the ring closure in place of formic acid. This proposed method has the advantage of requiring a relatively small molar excess of formamide but has the disadvantage that considerably reduced yields and lower quality are incidental to its use.

The present invention provides a means for preparation of benzothiadiazine compounds by ring closure of the orthosulfamylaniline which provides good yields and high quality based on both the aniline derivative and on the material employed to effect the ring closure. This is accomplished by using a mixture of formic acid and another compound which may be formamide, dimethylformamide, dimethylacetamide, or dimethylsulfoxide. Formamide is the preferred material.

When the method of the invention is employed, the reduction in the amount of formic acid required to effect the ring closure is very considerable. Thus, by the method of the aforementioned patent, the molar ratio of formic acid to the sulfamylaniline is in excess of about 30 to 1 to obtain yields in the range of 80 to 90%. The method of this invention produces up to 97% yields with the use of a much smaller amount of formic acid, for example, a molar proportion of 4 moles of formic acid to 1 mole of the sulfamylaniline.

According to the invention, the ring closure is effected by admixing the sulfamylaniline, formic acid, and an amide or sulfoxide of the aforementioned group, and heating the resulting mixture at a temperature between 75° C. and 175° C. for a time sufficient to permit ring closure to occur. Advantageously, the temperature is in the range of 100–150° C., and the preferred range is 125–140° C. Lower temperatures than those mentioned can

be employed, such as room temperature but the reaction time increases appreciably at such low temperatures and accordingly, it will not normally be desirable to operate at such low temperatures.

The pressure for the reaction is not critical. Conveniently, atmospheric pressure is employed but reduced or increased pressure can be used. Appreciable amounts of the desired end product will be obtained in one-half hour but it is best to let the reaction continue for at least an hour and in four hours time the maximum yield ordinarily can be obtained.

The proportions of the formic acid and the amide or sulfoxide compound with respect to each other and the sulfamylaniline can be varied over a rather wide range. These proportions should be from one-half to ten moles of formic acid with respect to the sulfamylaniline and from one-half to ten moles of amide or sulfoxide compound. Preferably, from one to six moles of the formic acid and formamide or sulfoxide compound should be used for each mole of sulfamylaniline.

The invention will further be clarified by the following examples:

Example 1

To a solution of 25 g. O-sulfamylaniline (0.145 mole) in 25 ml. (0.323 mole) dimethylformamide at 125° C. was added 25 ml. (0.586 mole) 90% formic acid. The solution was heated 2 hours at 125°, cooled to 50° and the solid product precipitated from solution by slow addition of 200 ml. of water. The resulting slurry was cooled to 10°, and aged 1 hour under stirring at this temperature. The slurry was filtered, the cake washed with 50% methanol (v./v.), and the solid 1,2,4-benzothiadiazine-1,1-dioxide dried to constant weight. The yield was essentially quantitative.

Example 2

A solution of 25 g. of 2,4-di-sulfamylaniline in 25 ml. dimethylsulfoxide at 140° treated under conditions similar to those described in Example 1 in which formic acid is also present, yielded solid 7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, also in nearly quantitative yield.

Examples 1 and 2 also serve to illustrate other examples involving corresponding reactions in which formamide, and dimethylacetamide are used in combination with formic acid.

Example 3

A slurry of 37.5 g. (.131 mole) of purified 5-chloro-2,4-disulfamylaniline in 25 ml. (.586 mole) of 90% formic acid and 25 ml. of formamide (.633 mole) was heated at 125° C. During the heating, which was continued for 4 hours, a solution formed and thereafter a precipitate appeared. After the heating period, the mass was cooled to 50° C., 100 ml. of water was then added while stirring the mass, and the diluted mass was then cooled to 5° C. and aged for 1 hour at this temperature while being stirred. Following the aging, the diluted mass was filtered to separate the product benzothiadiazine compound as filter cake. The cake was washed with water and methanol and then dried to constant weight. This procedure yielded a crude desired product in the form of white crystals having M.P. 358.2° C. The crude product was purified and an overall yield of purified desired product (i.e. 6-chloro-7-sulfamyl-1,2,3-benzothiadiazine-1,1-dioxide) of 95.8% was obtained. The purified product was in the form of white crystals, M.P. 358.5° C.

$E^{1\%}_{1\,cm.} = 404$ at 279 mu.

Example 4

The process of Example 3 is carried out but about one

mole of the formic acid and about one mole of the formamide per mole of the aniline compound is employed.

Example 5

The process of Example 3 is carried out but about six moles of the formic acid and about six moles of the formamide per mole of the aniline compound is employed.

What is claimed is:

1. The process of producing a 1,2,4-benzothiadiazine-1, 1-dioxide compound which comprises mixing together at a temperature of from 75° C. to 175° C. for a period of from ½ to 4 hours, ortho sulfamyl aniline, formic acid and a compound selected from the groups consisting of formamide, dimethylformamide, dimethylacetamide and dimethylsulfoxide, said selected compound being present in the ratio of from one-half to ten moles of the sulfamylaniline, and the formic acid being present in the ratio from one-half to ten moles of the sulfamylaniline.

2. The process according to claim 1 in which the temperature is between 100 and 150° C.

3. The process according to claim 1 in which said selected compound is present in the ratio of from one to six moles of the sulfamylaniline, and the formic acid is present in the ratio of from one to six moles of the sulfamylaniline.

4. The process for producing 6-chloro-7-sulfamyl-1,2, 4-benzothiadiazine-1,1-dioxide which comprises mixing together 5-chloro-2,4-disulfamylaniline, from one to six moles of formic acid and from one to six moles of formamide, per mole of the aniline.

References Cited in the file of this patent

UNITED STATES PATENTS

2,809,194 Novello ---------- Oct. 8, 1957

OTHER REFERENCES

Freeman et al.: J. Org. Chem., vol. 16, p. 816 (1951).

Novello: J. Am. Chem. Soc., vol. 79, pp. 2028–2029 (1957).