Acta Chemica Scandinavica, 1994: 48:181 182
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904-213X

Short Communication

Dinitrogen Pentoxide–Sulfur Dioxide, a New Nitration System

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Bakke, J. M. and Hegbom, I., 1994. Dinitrogen Pentoxide–Sulfur Dioxide, a New Nitration System. – Acta Chem. Scand. 48: 181–182. © Acta Chemica Scandinavica 1994.

A variety of methods are available for the nitration of aromatic compounds.[1–3] Nevertheless, the direct nitration of a number of substances gives low yields and the substitution has to be conducted by the initial preparation of suitably activated derivatives. This is, for instance, the case for a number of heteroaromatic compounds.

Dinitrogen pentoxide is one of the most powerful agents for electrophilic aromatic nitration and it has been used in a number of cases.[4] However, owing to its inaccessibility it has not been employed to any great extent in synthetic work. A few years ago, new preparative methods were reported,[5,6] making its use in preparative-scale nitrations more interesting. We have therefore made a study of its usefulness as a nitration agent for aromatic and heteroaromatic compounds. The results show that, under the right conditions, it is possible to obtain a high yield of nitroaromatic compounds that have been very difficult to obtain by standard methods.

Results and discussion

In Table 1 the results from nitrations under six sets of conditions are presented. These consist of N_2O_5 in HNO_3 and CCl_4, two solvents which have been much studied in this type of reaction. We have also investigated sulfur dioxide as a solvent; N_2O_5 in SO_2 is a combination which has not been used for nitrations before. For comparison, we have included the reactions with HNO_3 in SO_2 and with 'mixed acid' (HNO_3–H_2SO_4), the standard method for nitration of aromatic compounds. Pyridine and toluene were also reacted with $NO_2 \cdot BF_4$ in SO_2.

We chose six compounds for this introductory study: toluene, dimethyl and diethyl isophthalate, pyridine and 2- and 4-methylpyridine. Toluene represents activated aromatic systems and the two isophthalate esters are deactivated for electrophilic aromatic substitution. All three can be nitrated by the 'mixed acid' method although hydrolysis of the esters during work-up of the strongly acidic reaction mixture must be expected. Pyridine, 2- and 4-methylpyridine are compounds that virtually cannot be nitrated at all under standard conditions.

The results in Table 1 confirm earlier reports on nitrations in HNO_3–H_2SO_4. The isophthalate esters were nitrated in moderate yields, and pyridine and the methylpyridines not at all. Dinitrogen pentoxide in nitric acid gave slightly better yields for the isophthalates than did the 'mixed acid' method. Carbon tetrachloride is taken as an example of an aprotic solvent. The reactions of the isophthalates with N_2O_5 in this solvent gave lower yields than with N_2O_5 in HNO_3. In aprotic organic solvents with N_2O_5, radical reaction mechanisms compete with the electrophilic mechanism (via NO_2^+) which predominates in solvents such as HNO_3.[4] Dinitrogen pentoxide in CCl_4 or HNO_3 gave complex reaction mixtures with pyridine.

Only one of the six nitration systems in Table 1 gave results which were very different from those already reported: the combination of dinitrogen pentoxide and sulfur dioxide. From Table 1 it appears that we have a new nitration system which—at least for some compounds—gives much better results than the traditional ones. This is clear from the results of the nitration of pyridine and methylpyridines where 51–69% of the corresponding nitro compounds were obtained The direct nitration of these compounds has been virtually impossible before. Direct nitration of pyridine with nitric acid–sulfuric acid gave 3% of 3-nitropyridine.[7] Potassium nitrate and fuming sulfuric acid at 330°C has been claimed to give 15% 3-nitropyridine,[8] although this procedure gave only 1% yield in the hands of other workers.[9] The same reactants at 160°C gave 2% 2-methyl-5-nitropyridine from 2-methylpyridine.[10] This compound has therefore been made by a multistep synthesis starting from 2-aminopyridine.[11] Nitration of pyridine in the 4-position can be obtained by nitration of pyridine 1-oxide followed by removal of the *N*-oxygen.[12] In the direct nitration of pyridine, the *N*-nitration is believed to be the reason for the low yields. To avoid this, attempts have been made to block this position. Several attempts have

Table 1. Comparison of different nitration methods. Nitrating agent (25 mmol) and substrate (12.5 mmol) were dissolved in the reaction medium (25 ml). The yields are as isolated products except where otherwise stated. For details, see the Experimental.

Compound	Nitration method, yields (%)					
	HNO_3–SO_2	N_2O_5–SO_2	$NO_2 \cdot BF_4$–SO_2	N_2O_5–HNO_3	N_2O_5–CCl_4	HNO_3–H_2SO_4
Toluene		87[a,b]	74[a,c]			69[a,d]
Dimethyl isophthalate[e]	5[a]	90		69	30[a]	61
Diethyl isophthalate[e]	No reaction	80		79	20[a]	56
Pyridine	Mixture	60[f]	No reaction	Mixture	Mixture	3[7]
2-Methylpyridine		69[g]				2[h]
4-Methylpyridine		51[i]				

[a]Yield by GC/internal standard method. [b]*o*-Nitrotoluene 7%, *m*-nitrotoluene 1%, *p*-nitrotoluene 8%, 2,4-dinitrotoluene 56%, 2,6-dinitrotoluene 15%. [c]*o*-Nitrotoluene 22%, *m*-nitrotoluene 1%, *p*-nitrotoluene 17%, 2,4-dinitrotoluene 25%, 2,6-dinitrotoluene 9%. [d]2,4-Dinitrotoluene 59%, 2,6-dinitrotoluene 10%. [e]Products 5-nitroisophthalates. [f]Product 3-nitropyridine. [g]2-Methyl-5-nitropyridine:2-methyl-3-nitropyridine 91:9. [h]With KNO_3–H_2SO_4.[10] [i]Product 4-methyl-3-nitropyridine.

been made to obtain 3-nitropyridine, for instance by 2,6-disubstitution to block sterically the 1-position.[13] However, the reported attempts show that the yield of the disubstituted 3-nitropyridine is low and also that the removal of the auxiliary 2,6 substituents may be difficult. In conclusion on this point, the introduction of a nitro group into the pyridine ring has been difficult and the method presented here may be of some importance in this field.

The results from the nitration of the isophthalate esters show that the N_2O_5–SO_2 system may also be of value for the nitration of other aromatic systems: the method gave excellent yields of the 5-nitroisophthalate esters. With toluene, N_2O_5 was more reactive than $NO_2 \cdot BF_4$: a ratio of ca. 4:1 of dinitrotoluene:nitrotoluene was obtained with N_2O_5–SO_2 against 0.9:1 with NO_2BF_4–SO_2 (in both cases a 2:1 ratio of nitration agent:substrate was used).

Sulfur dioxide is surprisingly easy to handle: with a boiling point of −11°C it can be condensed, recycled or evaporated in standard laboratory equipment. However, the use of an effective fume cupboard is recommended.[14]

The results show that the new nitration system, dinitrogen pentoxide–sulfur dioxide is powerful and makes it possible to nitrate very deactivated aromatic compounds in good yields.

Experimental

Materials. Dinitrogen pentoxide was prepared by dehydration of fuming nitric acid ($d = 1.52$) with phosphorus pentoxide under an atmosphere of O_2–O_3.[15] It could be stored at −20°C for at least two weeks. Dimethyl and diethyl isophthalate were prepared by H_2SO_4-catalysed esterification of isophthalate with the respective alcohols. Sulfur dioxide was condensed directly from a steel cylinder (Norsk Hydro A/S) at −78°C and used without further purification. Pyridine was distilled from KOH prior to use. The other compounds were commercially available and were used as received.

General procedure for nitration with HNO_3 and N_2O_5. The nitration mixture was prepared by the addition of fuming nitric acid (1.0 ml, 24 mmol) or dinitrogen pentoxide (2.7 g, 25 mmol) to sulfur dioxide (25 ml) at −78°C. The substrate (12.5 mmol) was then added slowly. The mixture was warmed to −11°C over a period of 2 h, stirred for another 2 h and then poured over ice. Neutralisation ($NaHCO_3$), extraction (CH_2Cl_2), drying (Na_2SO_4) followed by evaporation gave the products. If necessary, the product was recrystallised. The nitrations in other solvents followed this general procedure except for the reaction temperature (ambient temperature). $NO_2 \cdot BF_4$ was weighed into the reaction flask in a dry box.

Acknowledgments. NTNF and Norsk Hydro A/S are thanked for their generous support of this work.

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Received June 7, 1993.