Pergamon

Tetrahedron Letters 39 (1998) 7243–7246

TETRAHEDRON
LETTERS

A Facile Reduction of Aromatic Nitro Compounds to Aromatic Amines by Samarium and Iodine

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Received 15 June 1998; revised 16 July 1998; accepted 17 July 1998

Abstract: *A simple method for the reduction of aromatic nitro compounds to aromatic amines was developed using samarium and catalytic amounts of iodine.* © 1998 Elsevier Science Ltd. All rights reserved.

Amines are extensively distributed in nature and have wide range of biological activity.[1] Reduction of the aromatic nitro compounds by catalytic hydrogenation[2] is probably the best method known to produce the aromatic amines although various other synthetic methods have appeared in the literature.[3]

As part of our experimental goal of synthesizing polycyclic compounds with anticancer properties, we became interested in developing a general method for synthesizing aromatic amines. We have noted a method involving reduction of the aromatic azido groups to the aromatic amines by metallic samarium[4] and iodine. One of us was previously involved in iodine catalyzed[5] reactions. We have also noted the reduction of aromatic azido compounds to amino compounds by various other methods.[6] However, aromatic azido compounds, particularly in polycyclic series, are not naturally abundant, are difficult to make, and in some cases need to be handled with care because of their sensitivity to metallic objects.[7] On the other hand, aromatic nitro compounds are easily accessible by conventional nitration, and many of them are commercially available. We wish to demonstrate here a simple reduction of such compounds by samarium and iodine.

First, several monocyclic benzene derivatives were chosen for this reduction study. Thus, reduction of *4*-nitroanisole (entry 1) to *4*-anisidine was achieved in refluxing methanol by using samarium and catalytic amounts of iodine (Scheme). From a series of experiments, we found that 4-equivalents of samarium were required for completion of the reaction. An increase in the amount of samarium did not reduce the time required. The reaction time under sonication remained the same. We found catalytic amounts of iodine to be necessary because the reduction did not proceed in the presence of samarium and methanol only. We also found that THF could be used as the solvent in some cases (entry 3 and 5) with equal effectiveness. Subsequently, we used several bicyclic and polycyclic nitro compounds for reduction under identical conditions and isolated the corresponding amino compounds in good yield. The results are presented in the table.

PII: S0040-4039(98)01555-X

Scheme

$$\mathrm{ArNO_2} \xrightarrow[\mathrm{CH_3OH}]{\mathrm{Sm,\ I_2\ (cat.)}} \mathrm{Ar\ NH_2}$$

60-94%

Table

Entry	Substrate	Product	Yield %[a]	Reflux Time[b]
1	4-nitroanisole	4-anisidine	88	7
2	4-bromonitrobenzene	4-bromoaniline	86	3
3	2-nitro ethylbenzoate	2-amino methylbenzoate	86	5
4	1-nitronaphthalene	1-aminonaphthalene	64	8
5	2-nitrofluorene	2-aminofluorene	95	7
6	2-nitro-9-ketofluorene	2-amino-9-ketofluorene	60	6
7	6-nitrochrysene	6-aminochrysene	94	8
8	1-nitropyrene	1-aminopyrene	92	7
9	12-nitro-6-acetamidochrysene	12-amino-6-acetamidochyrysene	64	48

a: isolated yield b: reaction time (in hr)

The table shows some selectivity in the reduction process. Thus, there is no dehalogenation (entry 2) or hydrogenolysis (entry 6). The widely used catalytic hydrogenation gives dehalogenation and hydrogenolysis in most of the reactions. 2-Nitroethylbenzoate (entry 3) gave 2-aminomethylbenzoate arising from a transesterification reaction in the presence of methanol. On the other hand, 2-aminoethylbenzoate was the product in the presence of THF.

A representative procedure is as follows: To 50 mg of the nitro compounds in 5 mL of dry methanol were added 4 equivalents of samarium and 0.1 equivalent of iodine and the mixture was refluxed under argon atmosphere until the starting material disappeared as indicated by TLC. The reaction mixture was diluted with 30mL of dichloromethane and filtered. The filtrate was washed with saturated aqueous sodium thiosulfate solution and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by crystallization from dichloromethane-hexanes or by column chromatography over basic alumina.

In order to compare the effectiveness of this samarium-induced reduction process with that of the well-established samarium diiodide[8] mediated reduction process, we carried out the reduction of 2-nitrofluorene (entry 5), 6-nitrochrysene (entry 7) and 1-nitropyrene (entry 8) with 8-10 equivalents of commercially available samarium diiodide solution in THF using 2% methanol[8d] and observed 60-80% conversion. We isolated 15-20% unreacted starting materials from the crude reaction mixtures by column chromatography. The isolated yield of the products from the same reaction under metal samarium-iodine induced condition was 92-95%

(Table). Samarium diiodide can be prepared by refluxing overnight equimolar samarium and iodine in THF.[9] As can be seen from the table, the reduction of several nitro compounds was completed within 3-8 h although we used catalytic amounts of iodine. Samarium diiodide is available in sealed bottle but can be inactivated even after a brief exposure to air and or moisture. As a result, we required different amounts of samarium iodide-THF solution for the reduction of the same nitro compound under identical conditions from a bottle which we used at an one month interval. The high reactivity of the metallic samarium is probably a result of the high reducing power as shown by the reduction potential data[4] ($Sm^{3+}/Sm = -2.41V$ vs $Sm^{3+}/Sm^{2+} = -1.55V$). Moreover, the method by inexpensive samarium and iodine is very convenient and comparatively easy to handle with respect to SmI_2 induced reduction method. Thus, we suggest that freshly prepared reducing agent from samarium and catalytic amounts of iodine is a better reagent than commercially available samarium diiodide.

Use of some salts and Lewis acids[10] in some cases produced hydroxyl amine derivatives under samarium-iodine induced reduction conditions. Prolonged reaction time or drastic conditions did not alter the product distribution. However, no hydroxyl amine derivatives were observed in the present reduction method by samarium-iodine. The intermediates, if any, may be transformed to the final amines very rapidly without building sufficient concentration.

In conclusion, we have shown a simple method for the reduction of aromatic nitro compounds to amines in excellent yield.[11] Some of the polycyclic amines that we synthesized are versatile starting materials for the development of anticancer agents.[12]

ACKNOWLEDGEMENT

This work was supported in part by a grant from the Golden Family Fund for Cancer Research.

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