Heteroatom Chemistry
Volume 17, Number 2, 2006

Two-Step Syntheses of 3-Methyl and 3-Phenyl-1,2,4-Benzotriazines

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Received 8 July 2005; revised 14 November 2005

ABSTRACT: *3-Methyl-1,2,4-benzotriazine and some of its derivatives were prepared in moderate yields (50–70%) via a reductive cyclization by a PtO_2-catalyzed hydrogenation of the corresponding 2-nitrophenylhydrazones of the pyruvic acid. The latter compounds were obtained in yields higher than 90% by reacting 2-nitrophenylhydrazines with sodium pyruvate salt. Three 3-phenyl-1,2,4-benzotriazine compounds were also produced via a reductive cyclization by a Pt/C-catalyzed hydrogenation of their corresponding 2-nitrophenylhydrazono-ethers in high yields (>70%).* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:166–172, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20200

INTRODUCTION

The reductive cyclization of nitrophenylhydrazones has been widely used to afford nitrogen-based heterocyclic molecules. To name but a few, there are 4*H*-pyrazolo-[1,5-*a*]benzimidazoles [1], ethyl-(1,2,4-benzotriazine-3-yl)acetate and its derivatives [2], benzo[1,2-*b*:5,4-*b*′]bis(1*H*)-imidazo[1,2-*b*]pyrazoles [3], 1,2-dihydro-1,2,5-benzotriazepines [4], and 3,4-dihydropyridazino[1,6-*a*]benzoimidazoles [5]. Several pathways for the synthesis of 1,2,4-benzotriazines have been reported [6–12]. For example, 3-amino-1,2,4-benzotriazine was prepared in 57% yield by the reduction of 3-amino-1,2,4-benzotriazine 1-oxide with sodium dithionite, the latter oxide was obtained in 39% yield by reacting nitroaniline with cyanamide [13]. Various pathways for the synthesis of 3-phenyl-1,2,4-benzotriazine have been described [9,12,14–19]. It is enlightening to recall that the oxidized of 1,2,4,benzotriazines have been of special interest because of their potential antitumor activity [20,21]. Indeed, the synthesis of 3-amino-1,2,4-benzotriazine-1,4-oxide, also known as tirapazamine, is nowadays a central occupation for many workers [22–24]. Accordingly, 1,2,4-benzotriazines are valuable precursors to very promising cancer therapeutic molecules.

In continuation of our work on heterocyclic synthesis [5], we developed short pathways to produce 3-methyl and 3-phenyl-1,2,4-benzotriazines from phenylhydrazones and phenylhydrazono-ethers, respectively. The hydrazones have been used largely as starting materials in the Fischer' indole synthesis [25].

EXPERIMENTAL

Apart from the starting material for the synthesis of **1a** and **3a**, which was purchased from Aldrich, the remaining phenylhydrazines were synthesized

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