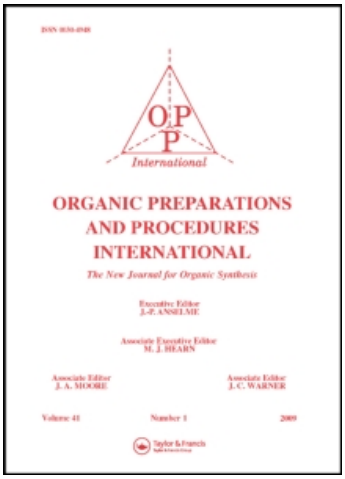

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A RELIABLE MULTI-KILOGRAM PREPARATION OF 4-PHENYLURAZOLE

B. Chandrasekhar[a]; G. B. Kumar[a]; S. Mallela[a]; S. B. Bhirud[a]
[a] Process Research and Development, Glenmark Research Centre, T.T.C. Industrial Area, Navi Mumbai, INDIA

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OPPI BRIEFS

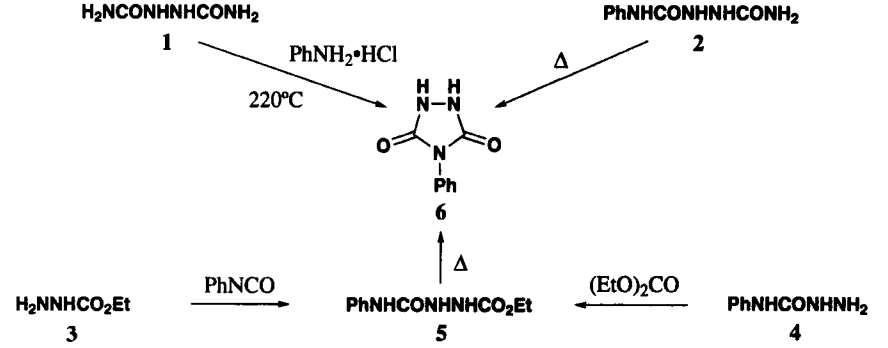
A RELIABLE MULTI-KILOGRAM PREPARATION OF 4-PHENYLURAZOLE

Submitted by B. Chandrasekhar*, G. B. Kumar, S. Mallela, and S. B. Bhirud
(06/30/04)

Process Research and Development, Glenmark Research Centre,
T.T.C. Industrial Area, MIDC Mahape, Navi Mumbai-400709, INDIA
E-mail: Chandrasekhar@glenmarkpharma.com
Telephone: 91-22-55902491. Fax: 91-22-55902318

4-Phenyl-1,2,4-triazolidine-3,5-dione commonly known as 4-phenylurazole (**6**), exhibits a wide range of useful properties such as anti-foggants,[1] stabilizers in color photographic emulsion,[2] additives in lubricants,[3] agents for controlling hyperlipidemia,[4] and bronchodilators.[5] The oxidation of 4-phenylurazole to the corresponding triazolinedione was reported as early as in 1894 by Thiele,[6] then later by Stolle[7] in 1912. The chemistry of triazolinediones is similar to that of α-carbonylazo compounds and recently the syntheses of novel heterocyclic compounds utilizing urazoles by photochemical reactions has been reviewed.[8] These properties have generated interest among synthetic organic chemists, leading to the development of several procedures.[9]

Several routes have been described for the preparation of 4-phenylurazole (**6**, *Scheme 1*). Antonio[9a] and Arndt[9b] obtained **6** by heating biurea (**1**) with aniline hydrochloride at 220°C (*route a*). However, in our hands the method was unreliable as decomposition began to occur at 220°C; moreover, the aniline hydrochloride also interferes with the isolation of the desired product. 4-Phenylurazole has also been prepared by heating the phenylbiurea **2** but the results



Scheme 1

were difficult to reproduce (*route b*).[9c] 4-Substituted urazoles have more generally been prepared by cyclization of 1-carbethoxy-4-substituted semicarbazides. 1-Carbethoxy-4-phenylsemicarbazide (**5**), the most common precursor of **6** (*route c*), has been obtained by treatment of ethyl carbazate (**3**) with phenyl isocyanate or by reaction of 4-phenylsemicarbazide (**4**) with diethyl carbonate.[9d] However, the latter method is not practical and economical for scale-up as 4-phenylsemicarbazide is expensive.

The preparation of 1-ethoxycarbonyl-4-phenylsemicarbazide (**5**) was reported by Zinner[9e] and then by Cookson.[9f] However, the method involves the fractional distillation of ethyl carbazate (**3**) from the by-products, ethanol and water, in the first step reaction of hydrazine monohydrate and diethyl carbonate. In addition, the reaction of **3** with phenyl isocyanate was performed in benzene as solvent. Mallakpour[9g] has reported the synthesis of 1-ethoxycarbonyl-4-phenylsemicarbazide from **3** with phenyl isocyanate in toluene as a solvent instead of benzene, without solving the operational problems associated with fractional distillations. 4-Phenylurazole (**6**) was also prepared by the cyclization reaction of **5** in 4 M KOH, followed by acidification with conc. hydrochloric acid. In our hands, the recrystallization involved in these methods was lengthy and provided the product **6** contaminated with 2-5% potassium chloride. The reference sample procured from Merck-Germany (Batch. No.: S26489840) supported this fact.

We now report an efficient, rapid, high yielding method for the preparation of 4-phenylurazole, which constitutes a significant improvement in terms of yield, quality of the product and ease of work-up over previous procedures; it avoids fractional distillation at an intermediate stage as well as crystallization at the final stage. Compound **3** was thus prepared from reaction of 1 equiv. of diethyl carbonate with 1 equiv. of hydrazine monohydrate and the product was extracted from the reaction mixture by toluene. The product was reacted further with phenyl isocyanate and thus provided a quantitative yield of **5** after work up. 4-Phenylurazole obtained after cyclization reaction of **5** with KOH and subsequent acidification with HCl, was washed with water, yielding a KCl free solid, which was found to be pure by HPLC, DSC, MS, ^{13}C and ^{1}H-NMR. This material could be used as such for further transformations.[10a,b] We believe this to be the method of choice for the multi-kilogram preparation of this useful intermediate.

EXPERIMENTAL SECTION

Solvents and reagents were obtained from commercial sources and were used as such without any further purification unless specified. Hydrazine hydrate was handled using personal protection equipment in a ventilated hood as it is a carcinogen. The melting points were recorded on Mettler Toledo FP90 apparatus and are uncorrected. The ^{1}H NMR spectra were obtained using a 300 MHz Varian spectrometer using tetramethylsilane as internal standard. Infrared spectra were recorded using a Perkin-Elmer spectrum1 instrument. Mass spectra were recorded on an Applied Biosystem API 3000. HPLC analysis was performed using a Shimadzu LC-8A, UV-vis detector, SPD-10A, *VP*data module, and a Hypersil C^{18} column.

Preparation of 1-Ethoxycarbonyl-4-phenylsemicarbazide (5).- Hydrazine monohydrate (1,200 g, 24 mol) and (3,500 g, 29.66 mol) of diethyl carbonate was suspended in a 20 L four neck round-bottom flask. The reaction mass was stirred and heated to 90-95°C for a period of 4-5 h. The progress of the reaction was monitored by GC. The mixture was cooled to room temperature and the resulting mixture was extracted with toluene (6 x 4 L), and it was washed with water (4 x 5 L).The combined toluene layer was suspended in a 50-L reactor. The reaction mixture was cooled to 5-10°C and then 2,860 g. (24.03 mol) of phenyl isocyanate was added at 5-10°C in about 45 min. After completion of addition, the reaction mixture temperature was raised to 25-30°C in about 2 h and heated to 80-85°C for 2 h. The precipitated solid was collected and dried to furnish 5,170.0 g (97%) of 1-ethoxycarbonyl-4-phenylsemicarbazide (**5**), mp. 151-152°C, (*lit.*[9f] 154-155°C). The product was not purified further for use in the next step. IR (KBr): 3300, 1800, 1690, 1645 cm^{-1}.

Preparation of 4-Phenylurazole (6).- 1-Ethoxycarbonyl-4-phenylsemicarbazide (**5**) (5,170 g, 24.50 mol) and 11.65 L of 4M potassium hydroxide solution were placed into 50-L reactor. The reaction mixture was stirred and heated to 80-90°C for 1-2 h, the progress of the reaction was monitored by TLC [Precoated aluminium sheets with silica gel 60 F_{254}, 0.2 mm thickness, Merck cat. no. 1.05554]. The hot solution was filtered on Celite bed to remove the insoluble particles by applying vacuum. After cooling to room temperature, the filtrate was acidified with conc hydrochloric acid (3.85 L) to pH 2.5-3. The precipitated 4-phenylurazole was collected, washed with water (3 x 10 L) and dried to afford 3,900 g (23.92 mol) of (**6**), yield 95%, purity >99.5% as determined by HPLC, [HPLC system: Inertsil ODS 3V, C^{18} 250 mm column; mobile phase: 0.01M n-$Bu_4(NH_4)_2SO_4$/MeCN in 80:20 ratio, flow rate 1 mL/min; UVλmax 220 nm, retention time 5.6 min], mp 209-210°C (*lit.*[9f] 209-210°C). IR: (KBr): 3165, 1685 cm^{-1}. ^1H NMR: (DMSO d_6) δ 7.35-7.55 (m, 5H), 10.8 (s, 2H). ^{13}C NMR: (DMSO d_6) δ 126.4, 127.9, 129.1, 132.1, 153.7. MS: m/z 177 corresponding to $C_8H_7N_3O_2$.

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A CONVENIENT METHOD FOR PREPARATION OF TRIAZOLINEDIONES

Submitted by (06/15/04) Abdol Reza Hajipour* and Morteza Malakoutikhah

Pharmaceutical Research Laboratory, College of Chemistry
Isfahan University of Technology, Isfahan, 84156, IR IRAN
e-mail: haji@cc.iut.ac.ir

4-Substituted-1,2,4-triazoline-3,5-diones are very important because of their ability to participate in concerted and stepwise reactions.[1-4] These compounds have been used in electrophilic aromatic substitution,[5] as dehydrogenation agents[6] and in the oxidation of alcohols to aldehydes and ketones.[7] Since they are very reactive and sensitive to heat and to the oxidizing agents used to generate them, the preparation of these compounds is difficult. Most of the reported reagents for the oxidation of urazoles to the corresponding triazolinediones lead to the