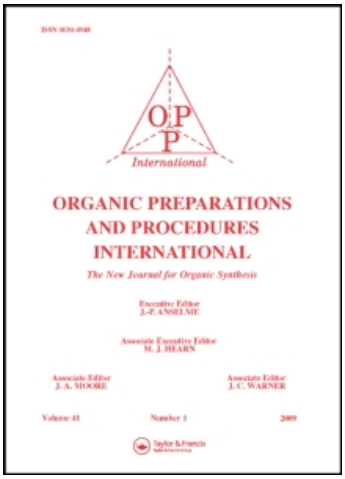

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A CONVENIENT SYNTHESIS OF N-5-(1,1-DIMETHYLETHYL)-3-ISOXAZOLYL-N,N-DIMETHYLUREA

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A CONVENIENT SYNTHESIS OF N-5-(1,1-DIMETHYLETHYL)-3-ISOXAZOLYL-N,N-DIMETHYLUREA

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(11/05/84)

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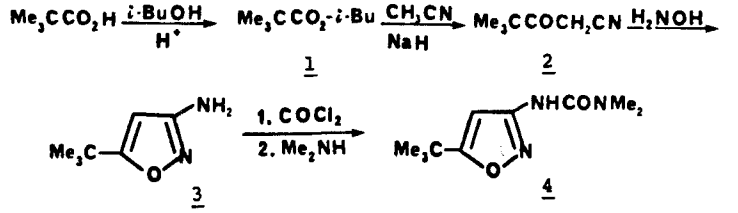
A practical and economical synthesis of N-5-(1,1-dimethylethyl)-3-isoxazolyl-N,N-dimethylurea (4),[1] directly from pivalic acid without isolation of intermediates has been developed. This preparation offers the advantage that large scale reactions can be performed economically and efficiently



Pivalic acid was esterified to isobutyl pivalate with isobutyl alcohol in cyclohexane in nearly quantitative yield.[2] Treatment of 1 with acetonitrile and sodium hydride in cyclohexane afforded pivaloylacetonitrile (2) in 85% yield.[2,3] Reaction of the ketonitrile (2) with hydroxylamine sulfate in water proceeded smoothly to afford 5-t-butyl-3-aminoisoxazole (85%); the major side-product in this cyclization was the 3-t-butyl-5-aminoisoxazole which was hydrolyzed to 3-t-butyl-5(4H)-isoxazolone under the reaction conditions; it was removed by base work-up.[4] The desired product was obtained in 63% overall yield by treatment of (3) with phosgene ad gaseous dimethylamine. The major impurity of this reaction was the symmetrical isoxazolyl urea whose formation could be greatly reduced by adding the aminoisoxazole to phosgene.

EXPERIMENTAL SECTION

N-5-(1,1-Dimethylethyl)-3-isoxazolyl-N,N-dimethylurea (4).- A mixture of 51 g (0.5 mole) of pivalic acid, 37 g (0.5 mole) of isobutyl alcohol, 100 ml of cyclohexane and 1.3 g of conc. sulfuric acid was refluxed for 5 hrs. while water was azeotropically removed. The mixture was then cooled to 30°, washed successively with two 100 ml portions of water, two 25 ml portions of saturated aqueous sodium bicarbonate, and two 50 ml portions of water. The cyclohexane solution containing the isobutyl pivalate was then azeotropically dried and cooled.

Then to a suspension of 26.4 g (0.57 mole) of sodium hydride (50% dispersion in mineral oil) in 640 ml of cyclohexane at reflux was added dropwise the solution of isobutyl pivalate obtained above to which had been added 28.7 g (0.7 mole) of acetonitrile. The rection mixture was heated at reflux for 7 hrs., cooled to room temperature and water (50 ml) was added. The cyclohexane layer was discarded and the aqueous

layer acidified with conc. hydrochloric acid (128 ml). The resulting acidified aqueous layer was extracted with two 300 ml portions of toluene and the combined toluene layers washed with 100 ml saturated sodium bicarbonate solution. To the toluene solution was added 37 g of 50% aqueous sodium hydroxide and 240 ml of water. The toluene layer was discarded and the aqueous phase was mixed with a solution containing hydroxylamine sulfate (36.2 g, 0.22 mole) and water (160 ml). This solution was heated to 70° for 4 hrs., conc. hydrochloric acid (111 ml) was added and the reaction mixture was heated at 70° for an additional 70 min., cooled to room temperature and extracted with 125 ml of cyclohexane. The cyclohexane layer was discarded and the aqueous phase was treated with 50% aqueous sodium hydroxide (80 ml) between 25-35° and was extracted with two 300 ml portions of ethyl acetate. The aqueous layer was discarded and the combined ethyl acetate layers washed with 150 ml of saturated sodium chloride solution and dried over magnesium sulfate. The drying agent was removed by filtration and washed with 100 ml of ethyl acetate. A total of 450 ml of ethyl acetate was removed by distillation from the combined ethyl acetate solution.

The concentrated acetate solution was then added to a solution containing 27 ml of phosgene in 150 ml of ethyl acetate at -15° over a period of 35 min. and allowed to warm to room temperature; the mixture was refluxed for 90 min. To this cooled solution (25°) was added dropwise, 36 ml of dimethylamine. The mixture was refluxed for 2 hrs., cooled to room temperature and neutralized by the addition of 24 ml of 1N hydrochloric acid. The layers were separated and the ethyl acetate layer was dried over magnesium sulfate; magnesium sulfate was removed by filtration and ethyl acetate (385 ml) was removed by distillation. The hot ethyl acetate solution was poured into 700 ml of water and cooled to

5°. The precipitated product was collected to afford 66.2 g (63%) of N-5-(1,1-dimethylethyl)-3-isoxazolyl-N,N-dimethylurea (4), mp. 114-116°. H^1NMR($CDCl_3$): δ 1.31 (s, t-butyl), 3.06 (s, 6, N-CH), 6.66 (s, 1, C-H), 8.63 (s, 1, N-H). Mass spectrum: M^+ 211.

Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89

Found: C, 56.63; H, 8.04; N, 19.69

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2. This reaction proceeds equally well in toluene.

3. Methyl pivalate may be used instead of isobutyl pivalate.

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