Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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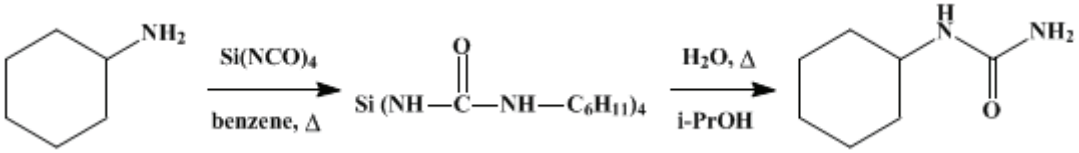
N-MONO- AND N,N-DISUBSTITUTED UREAS AND THIOUREAS

Submitted by Roy G. Neville[1] and John J. McGee[2].
Checked by William E. Parham and J. Kent Rinehart.

1. Procedure

METHOD I
CYCLOHEXYLUREA

[Urea, cyclohexyl-]

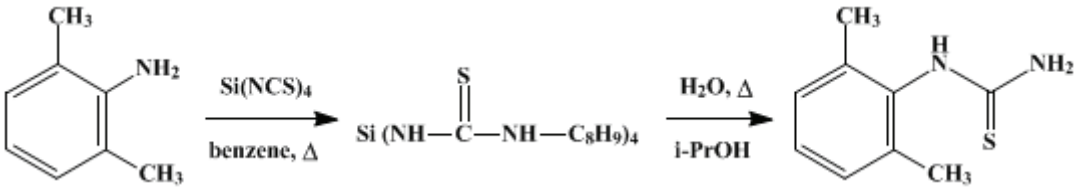


A solution of cyclohexylamine (39.7 g., 0.4 mole) (Note 1) in 100 ml. of anhydrous benzene (Note 2) is added slowly to a stirred solution (Note 3) of silicon tetraisocyanate (19.6 g., 0.1 mole) (Note 4) in 150 ml. of anhydrous benzene contained in a 1-l. round-bottomed flask. After the exothermic reaction has subsided, the mixture is heated at the reflux temperature for 30 minutes; the benzene is then removed using a rotary evaporator. Dilute isopropyl alcohol (200 ml.) (Note 5) is added to the residue, and the resulting mixture is heated at the reflux temperature for 30 minutes. The hot mixture is filtered through a 0.5-in. layer of Celite® contained in a coarse-grade sintered-glass funnel (Note 6). The gelationous silica is washed with two 75-ml. portions of acetone and is then pressed and drained. The combined filtrates are evaporated to dryness on a steam bath (Note 7). The crude cyclohexylurea (m.p. 185–191°, 55.0 g., 97% yield) is recrystallized from 220 ml. of isopropyl alcohol (Note 8) to give 37 g. (65%) of product, m.p. 192–193°. Concentration of the mother liquor affords about 9 g. (16%) of additional product which is less pure (m.p. 189–192°) (Note 9).

1. Procedure

METHOD II
2,6-DIMETHYLPHENYLTHIOUREA

[Urea, 1-(2,6-dimethylphenyl)-2-thio-]



Silicon tetraisothiocyanate (26.0 g., 0.10 mole) (Note 10) is finely ground under 100 ml. of anhydrous benzene, and the mixture is quickly transferred to a 1-l. round-bottomed flask. The mortar and pestle are washed with two 25-ml. portions of anhydrous benzene, and the washings are added to the flask. A solution of 2,6-dimethylaniline (48.5 g., 0.4 mole) (Note 1) in 100 ml. of anhydrous benzene is added to the well-stirred mixture. The reaction is mildly exothermic. The mixture is heated at the reflux temperature for 30 minutes, and the benzene is then removed using a rotary evaporator. Dilute isopropyl alcohol (200 ml.) (Note 5) is added to the residue, and the resulting mixture is heated at the reflux temperature for 30 minutes. The mixture is then processed in exactly the same manner as described above for the preparation of cyclohexylurea. The crude 2,6-dimethylphenylthiourea (m.p. 193–197°, 71.3 g., 99% yield) is recrystallized from 280 ml. of isopropyl alcohol (Note 8) to give 50 g.

(72%) of product, m.p. 201–202°. Concentration of the mother liquor affords 11 g.. (15%) of less pure product, m.p. 197–199° (Note 11).

2. Notes

1. Cyclohexylamine and 2,6-dimethylaniline were obtained from Eastman Organic Chemicals and were redistilled prior to use.
2. Benzene was dried over sodium wire.
3. The mixture becomes viscous; however, a good magnetic stirrer is adequate. The checkers found it convenient to decrease the viscosity of the mixture by increasing the volume of benzene from 100 ml. to 150–300 ml.
4. Silicon tetraisocyanate is prepared from silicon tetrachloride and silver cyanate or lead cyanate.[3,4]
5. Dilute isopropyl alcohol is prepared by mixing the alcohol (180 ml.) with water (20 ml.). The use of more than about 10% water in the alcohol results in an intractable mass of gelatinous silica from which it is very difficult to separate a good yield of the urea.
6. As gelatinous silica clogs the filter when too strong a suction is applied, it is best to carry out the filtration using very gentle suction. Only when almost all the liquid has passed through the filter is strong suction applied. The checkers used Hyflo Supercel® as the filter aid, and a 600-ml. coarse-grade sintered-glass funnel.
7. An open dish or a rotary evaporator is satisfactory.
8. Isopropyl alcohol is a good solvent to employ for recrystallizing most ureas; however, occasionally a mixture of alcohol and benzene or pure benzene is superior.
9. This material is of sufficient purity for most purposes. If a purer product is required, the first crop of the cyclohexylurea (37 g.) is recrystallized from 135 ml. of isopropyl alcohol to yield 23 g. of product, m.p. 195.5–196.0°
10. Silicon tetraisothiocyanate is prepared from silicon tetrachloride and silver thiocyanate[5,6] or, preferably, ammonium thiocyanate.[6,7] The silicon tetraisothiocyanate used by the checkers was slightly yellow; however, this did not affect the yield of product.
11. This material is of sufficient purity for most purposes. If purer material is required, the first crop of 2,6-dimethylphenylthiourea (50 g.) is recrystallized from 250 ml. of isopropyl alcohol to yield 41 g. of product, m.p. 203.5–204.0°.

3. Discussion

Cyclohexylurea has been prepared by the reaction of cyclohexyl isocyanate with gaseous ammonia[8] or ammonium hydroxide,[9] by thermal decomposition of cyclohexyl allophanamide,[10] by treating cyclohexylamine hydrochloride with an aqueous solution of potassium cyanate,[11] by heating nitrosomethylurea with cyclohexylamine,[12] and by heating an ethanolic solution of cyclohexylamine and 3,5-dimethyl-1-carbamylpyrazole.[13]

2,6-Dimethylphenylthiourea has been synthesized by allowing 2,6-dimethylaniline hydrochloride to react with ammonium thiocyanate.[14]

4. Merits of the Preparation

These procedures are generally applicable to aliphatic, alicyclic, aralkyl, aromatic, and heterocyclic primary or secondary amines. The reactions fail or give poor yields with sterically hindered amines such as 2-trifluoromethylaniline, 2,6-dibromoaniline, and diphenylamine. In general, however, excellent (95–100%) yields of N-mono- or N,N-disubstituted ureas or thioureas can be obtained by employing these versatile reactions which are, in most cases, superior to and supplement the methods conventionally employed for the synthesis of ureas and thioureas.[15] Because of the rapidity, ease, and excellent yields of these reactions, silicon tetraisocyanate and tetraisothiocyanate (both of which are readily prepared[4,6]) are likely to become standard reagents for the preparation of N-mono- and N,N-disubstituted ureas and thioureas. The submitters have employed these reagents to prepare large-scale (O.4*M*) amounts of the following compounds (yields in parentheses): benzylurea, m.p. 148° (96%);[16] phenylurea, m.p. 147° (95%);[17] *t*-butylurea, m.p. 182° (95%);[18] N-(2-benzothiazolyl)urea, m.p. >350° (95%);[19,20] dibenzylthiourea, m.p. 140° (95%);[21] *t*-butylthiourea, m.p. 168° (98%).[22] In addition, the scope and

limitation of the reactions of silicon tetraisocyanate and tetraisothiocyanate have been investigated with more than fifty alkyl, aralkyl, aromatic, and heterocyclic primary and secondary amines.[23,24]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-MONO- AND N,N-DISUBSTITUTED UREAS AND THIOUREAS

silicon tetraisocyanate and tetraisothiocyanate

ammonia (7664-41-7)

Benzene (71-43-2)

ammonium thiocyanate (1762-95-4)

acetone (67-64-1)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

ammonium hydroxide (1336-21-6)

Phenylurea (64-10-8)

potassium cyanate (590-28-3)

diphenylamine (122-39-4)

Nitrosomethylurea

cyclohexylamine (108-91-8)

2,6-Dibromoaniline (608-30-0)

silver cyanate (3315-16-0)

Cyclohexylurea,
Urea, cyclohexyl- (698-90-8)

silicon tetraisocyanate (3410-77-3)

Urea, 1-(2,6-dimethylphenyl)-2-thio-,
2,6-Dimethylphenylthiourea (6396-76-5)

Silicon tetraisothiocyanate (6544-02-1)

2,6-dimethylaniline (87-62-7)

silicon tetrachloride (10026-04-7)

silver thiocyanate (1701-93-5)

cyclohexyl isocyanate (3173-53-3)

cyclohexyl allophanamide

cyclohexylamine hydrochloride (4998-76-9)

3,5-dimethyl-1-carbamylpyrazole (934-48-5)

2,6-dimethylaniline hydrochloride (21436-98-6)

2-trifluoromethylaniline (88-17-5)

benzylurea (538-32-9)

N-(2-benzothiazolyl)urea

dibenzylthiourea

t-butylurea (1118-12-3)

lead cyanate

t-butylthiourea (7204-48-0)