Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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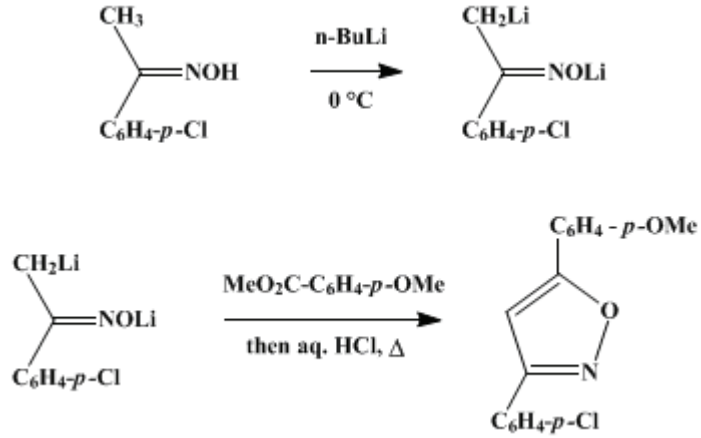
3-(4-CHLOROPHENYL)-5-(4-METHOXYPHENYL)ISOXAZOLE

[Isoxazole, 3-(4-chlorophenyl)-5-(4-methoxyphenyl)-]



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Checked by H. W. Jacobson and R. E. Benson.

1. Procedure

Caution! This preparation should be carried out in an efficient hood.

A 2-l., three-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen-inlet tube, and a 250-ml. pressure-equalizing dropping funnel attached to a calcium chloride tube is charged with 16.96 g. (0.1000 mole) of 4-chloroacetophenone oxime (Note 1) and 500 ml. of anhydrous tetrahydrofuran (Note 2). The flask is stoppered (Note 3) and cooled in an ice-water bath (Note 4). In the dropping funnel is placed 140 ml. (0.22 mole) of 1.6 *M* *n*-butyllithium in hexane (Note 5), which is rapidly added dropwise to the stirred solution over a 12–15-minute period. The solution is stirred for 30 minutes after the addition is complete, and the addition funnel is replaced by a clean one (125-ml. capacity), fitted with a calcium chloride drying tube (Note 6). Cooling is continued, a solution of 8.31 g. (0.0501 mole) of methyl anisate (Note 7) and (Note 8) in 100 ml. of anhydrous tetrahydrofuran is added to the stirred mixture over a 6–10-minute period, and the resulting mixture is stirred for an additional 30 minutes (Note 9). At the end of this period, 300 ml. of 3 *N* hydrochloric acid is added. The nitrogen-inlet tube is removed and replaced by a reflux condenser, and the dropping funnel is replaced by a ground-glass stopper. The ice bath is removed, and the mixture is heated under reflux for 1 hour. The flask is then cooled, and its contents are poured into a 2-l. Erlenmeyer flask, and solid sodium hydrogen carbonate is added to the mixture until neutralization is complete (Note 10).

The resulting mixture consists of an organic phase and a lower aqueous phase containing a small amount of insoluble material. The mixture is transferred to a 2-l. separatory funnel and the phases are separated. The aqueous phase is extracted with 100 ml. of tetrahydrofuran, which is combined with the original organic phase and concentrated to dryness on a rotary evaporator. Approximately 150 ml. of xylene is added to the flask and the contents of the flask are heated to reflux to remove any water present as the azeotrope. The resulting hot solution is filtered rapidly through a large Büchner funnel with light suction. The volume is reduced to approximately 100 ml., and the solution is cooled in an ice bath. The tan crystals which separate are collected in a Büchner funnel and washed with 10 ml. of ice-cold xylene. The crude product is recrystallized from 150 ml. of xylene (Note 11), yielding, after drying, 7.4–7.6 g. (52–53%) of 3-(4-chlorophenyl)-5-(4-methoxyphenyl)isoxazole, m.p. 175–176° (Note 12).

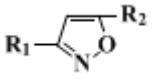
2. Notes

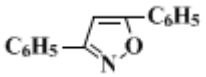
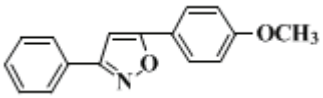
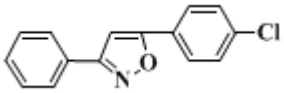
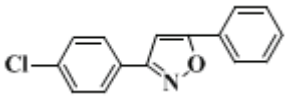
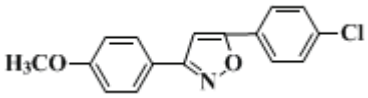
1. 4-Chloroacetophenone oxime was prepared by a modification of the method described by Shriner, Fuson, and Curtin.[4] A mixture of 100 g. (0.647 mole) of reagent grade 4-chloroacetophenone, 300 ml. of water, 200 ml. of aqueous 10% sodium hydroxide, 50 g. (0.72 mole) of hydroxylamine hydrochloride, and 500 ml. of ethanol is heated at reflux in a 2-l., round-bottomed flask for 2 hours. The crystals that separate on cooling in an ice bath are recovered by filtration and air dried. The product is added to approximately 1 l. of hexane, and the mixture is heated to reflux to remove any remaining water as the azeotrope. The resulting solution is cooled, yielding 70–74 g. (64–68%) of 4-chloroacetophenone oxime as white crystals, m.p. 96–97°.
2. Tetrahydrofuran was obtained from E. I. du Pont de Nemours and Company and distilled from lithium aluminum hydride or sodium-benzophenone immediately before use. The submitters used reagent grade tetrahydrofuran available from Matheson, Coleman and Bell.
3. Ground-glass stoppers proved most convenient.
4. The initial reaction of *n*-butyllithium (or lithium diisopropylamide) with the oxime is exothermic, and if the bath is not used, a slightly lower yield of colored product is obtained.
5. The concentration of the *n*-butyllithium obtained from Foote Mineral Company is generally close to the 1.6 *M* as quoted. An exact measurement of the volume (hypodermic syringe recommended) is not necessary, but a slight excess above the stoichiometrically required amount (0.20 mole) is needed. The submitters used *n*-butyllithium available from Lithium Corporation of America, Inc. A recent modification utilizes lithium diisopropylamide (0.33 mole) instead of *n*-butyllithium (0.22 mole).[5] A 0.33-mole sample of *n*-butyllithium is cooled to 0° and blanketed with nitrogen. To this base is added 0.33 mole of diisopropylamine dissolved in 150 ml. of tetrahydrofuran.
6. The purpose of the exchange is to provide a clean funnel for the addition of the ester solution. If the funnel is not changed, the yield is slightly lower. When lithium diisopropylamide is used the ratio of the reagents is 2 oxime: 6 base: 2 ester.
7. The ratio of the reagents is 2 oxime:4 base: 1 ester and is consistent with similar procedures used for a modified Claisen condensation.[6] The yield is based on the ester. When a ratio of reagents of 1 oxime: 2 base: 1 ester was used, a yield of 21% based on the ester was obtained.
8. Methyl anisate was obtained from Eastman Organic Chemicals.
9. At least 30 minutes is required for an optimum yield of the isoxazole.
10. Care should be taken to add the sodium hydrogen carbonate in small amounts initially, in order to avoid excessive frothing. The mixture was tested with pH paper to establish complete neutralization.
11. The product can also be recrystallized from ethanol, but a substantially larger volume of solvent is required.
12. The product has the following spectral properties; IR (KBr) $cm.^{-1}$: 3103 and 3006 (aromatic C-H), 2955, 2925, and 2830 (aliphatic C-H stretching), 1257 and 1032 (aromatic methyl ether), 841 and 812 (C-H out-of-plane bending of isoxazole C_4-*H* and 4-substituted phenyl); ^{1}H NMR (trifluoroacetic acid), δ (multiplicity, number of protons, assignment): 3.98 (s, 3H, OCH_3), 7.00–7.27 (m, 1H, isoxazole C_4-*H*; and 2H, aryl *H*), and 7.42–7.97 (m, 6H, aryl *H*).

3. Discussion

This procedure has several advantages over previous methods. It provides a simple, direct route to unsymmetrically substituted isoxazoles in which the location of substituents is unequivocal. The method uses readily available starting materials and can be used for the synthesis of a variety of substituted isoxazoles in which the substituents are stable to *n*-butyllithium. Examples of products synthesized by this method[7] are given in Table I.

TABLE I
ISOXAZOLES DERIVED FROM OXIMES[7]



R_1	R_2	Yield[a](%)
C_6H_5-	C_6H_5-	 59
C_6H_5-	4-$CH_3OC_6H_4$-	 51
C_6H_5-	4-ClC_6H_4-	 59
4-ClC_6H_4-	C_6H_5-	 65
4-$CH_3OC_6H_4$-	4-ClC_6H_4-	 66[b]

[a]Yield obtained using ~2.25 *M* *n*-butyllithium reagent.
[b]100% yield obtained using lithium diisopropylamide reagent.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)isoxazole has been prepared from the dilithio derivative of 4-chloroacetophenone oxime by three other methods: (a) reaction with anisonitrile (4-methoxybenzonitrile) followed by acid-catalyzed cyclization,[8] (b) reaction with *N,N*-dimethylbenzamide followed by acid-catalyzed cyclization,[9] and (c) condensation of the dilithio intermediate, prepared in an excess of lithium diisopropylamide, with methyl 4-methoxybenzoate, followed by acid-catalyzed cyclization.[6] The condensation of dilithioöxime with aroyl chlorides, followed by acid-catalyzed cyclization, could result in 4-acylisoxazoles.[10]

The use of dilithio reagents for the preparation of heterocyclic systems has been extended to the synthesis of 2-isoxazolin-5-ones[11] by carboxylation of a dilithioöxime, followed by cyclization, and the synthesis of pyrazoles from dilithiophenylhydrazones and trilithiothiohydrazones.[12,13] If the dilithiophenylhydrazones are formed in an excess of lithium diisopropylamide, they can be treated with diethyl carbonate, followed by cyclization to give 2-pyrazolin-5-ones.[14] Dilithioöximes formed in an excess of lithium diisopropylamide can be condensed with electrophilic-nucleophilic reagents such as methyl anthranilate.[15]

References and Notes

1. Submitted from William Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania 18015. [Present address: Department of Chemistry, Newberry College, Newberry, South Carolina 29108. Technical assistance by David C. Reames is acknowledged.]
2. National Aeronautics and Space Administration Trainee, 1967–1969.
3. Deceased January 6, 1970.

4. R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed., Wiley, New York, 1964, p. 289 (4th ed., 1956, p. 255).
5. T. D. Fulmer, L. P. Dasher, B. L. Bobb, J. D. Wilson, K. L. Sides, and C. F. Beam, *J. Heterocycl. Chem.*, **17**, 799 (1980).
6. C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 113 (1954).
7. C. F. Beam, M. C. D. Dyer, R. A. Schwarz, and C. R. Hauser, *J. Org. Chem.*, **35**, 1806 (1970).
8. C. F. Beam, R. S. Foote, and C. R. Hauser, *J. Heterocycl. Chem.*, **9**, 183 (1972).
9. G. W. Barber and R. A. Olofson, *J. Org. Chem.*, **43**, 3015 (1978).
10. R. M. Sandifer, L. M. Shaffer, W. M. Hollinger, D. C. Reames, and C. F. Beam, *J. Heterocycl. Chem.*, **13**, 607 (1976).
11. J. S. Griffiths, C. F. Beam, and C. R. Hauser, *J. Chem. Soc. C*, 974 (1971).
12. R. S. Foote, C. F. Beam, and C. R. Hauser, *J. Heterocycl. Chem.*, **7**, 589 (1970).
13. C. F. Beam, R. S. Foote, and C. R. Hauser, *J. Chem. Soc. C*, 1658 (1971).
14. J. D. Wilson, T. D. Fulmer, L. P. Dasher, and C. F. Beam, *J. Heterocycl. Chem.*, **17**, 389 (1980).
15. J. Brown, K. L. Sides, T. D. Fulmer, and C. F. Beam, *J. Heterocycl. Chem.*, **16**, 1669 (1979).

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

4-chloroacetophenone oxime

4-chloroacetophenone

sodium-benzophenone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

nitrogen (7727-37-9)

xylene (106-42-3)

Hydroxylamine hydrochloride (5470-11-1)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

diethyl carbonate (105-58-8)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

methyl anthranilate (134-20-3)

methyl anisate,
methyl 4-methoxybenzoate (121-98-2)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)isoxazole,
Isoxazole, 3-(4-chlorophenyl)-5-(4-methoxyphenyl)- (24097-19-6)

isoxazole (288-14-2)

anisonitrile,
4-methoxybenzonitrile (874-90-8)

N,N-dimethylbenzamide (611-74-5)