Stereoselective Synthesis of (*E*)-2-Hydroxyimino-2-phenylacetonitrile by Photolysis of 4-Azido-3-phenylfurazan 2-Oxide

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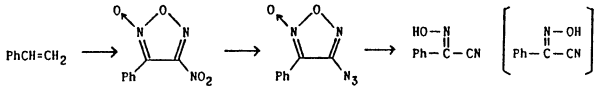
Synopsis. Synthesis of (*E*)-2-hydroxyimino-2-phenylacetonitrile from styrene was examined. This compound was obtained selectively by the photolysis of 4-azido-3-phenylfurazan 2-oxide.

Oximes are important intermediates for preparing various materials such as lactams, pharmaceuticals, pesticides, or polyamide fibers. Of these, 2-hydroxyimino-2-phenylacetonitrile (**3**) is the synthetic block of 2-(*t*-Butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), which is utilized as an excellent protecting agent in peptide syntheses[1]. In this paper, we should like to report a novel and stereoselective synthesis of (*E*)-2-hydroxyimino-2-phenylacetonitrile (**3a**) from styrene via the photolysis of 4-azido-3-phenylfurazan 2-oxide (**2**).



1 **2** **3a** **3b**

Experimental

Nitration of Styrene. To a solution of styrene (1.04 g, 10.0 mmol) in dichloromethane (50 cm^3), was added powdered sodium nitrite (80 mmol) with stirring. Acetic acid (80 mmol) was added over 30 min. After stirring for 2 h, hydrochloric acid (2 mol dm^{-3}, 30 cm^3) was added and the reaction mixture was stirred overnight. The dichloromethane layer was separated and concentrated. By chromatography on silica gel (hexane-dichloromethane, 2:3), 4-nitro-3-phenylfurazan 2-oxide (**1**) (1.41 g, 6.81 mmol, 68%) was isolated, mp 100.5—101.5 °C; lit. 100 °C.[2]

Substitution of 1 with Azide Ion. To a solution of sodium azide (34 mg, 0.52 mmol) in dimethyl sulfoxide (2 cm^3), **1** (52 mg, 0.25 mmol) was added. After 10 min, the solution was poured into an aq sodium dihydrogenphosphate solution. By extraction with dichloromethane and subsequent silica-gel TLC, 4-azido-3-phenylfurazan 2-oxide (**2**) (47.8 mg, 0.235 mmol, mp 95 °C, 94%) was isolated.

Decomposition of 2. a) Pyrolysis: A solution of **2** (102 mg, 0.502 mmol) in 1-pentanol (2 cm^3) was refluxed for 3 h. By evaporation of the solvent and subsequent silica-gel TLC (hexane-ethyl acetate,7:3), the two oximes, (*E*)- (**3a**, Rf 0.25, mp 100 °C, 11 mg, 0.075 mmol, 15%) and (*Z*)- (**3b**, Rf 0.30, mp 130 °C, 22 mg, 0.15 mmol, 30%) 2-hydroxyimino-2-phenylacetonitriles were isolated. **b) Photolysis:** A solution of azide **2** (80.0 mg, 0.394 mmol) in dichloromethane and ethanol (7:3, 50 cm^3) was irradiated through a Pyrex filter by a 500-W high-pressure mercury lamp under nitrogen for 25 min. Only the single isomer **3a** (54.0 mg, 0.369 mmol, 94%) was obtained.

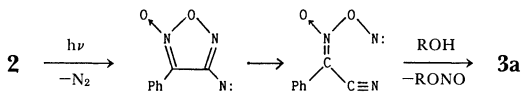
Successive Synthesis of 3a from Styrene. The nitration of styrene (5.0 mmol) was carried out in the same manner as described above. The dichloromethane layer was separated and transferred to an Erlenmeyer flask. Sodium azide (7.7 mmol) and 18-crown-6 (2.5 mmol) was added and the reaction mixture was stirred for 2 h. The solution was filtered through a short silica-gel column to remove inorganic salts and the crown ether. The eluate was diluted with dichloromethane and ethanol (7:3) and the volume was adjusted to 100 cm^3. Photolysis was carried out in the same manner as described above until most of the azide had disappeared. The solution was concentrated and chromatographed on silica gel to afford the oxime **3a** (3.0 mmol, 60% overall yield).

Results and discussion

The (*E*)-oxime **3a** is less stable thermodynamically than the corresponding *Z*-isomer **3b** and hence its selective synthesis has not been reported. For example, the oximes can be synthesized by nitrosation of phenylacetonitrile with alkyl nitrites, but a large excess of the (*Z*)-oxime is invariably formed.[3,4] The (*E*)-oxime is, therefore, not obtained by usual methods.[5] On the other hand, our method starting from styrene affords the (*E*)-oxime selectively.

The key compound in our method is 4-azido-3-phenylfurazan 2-oxide (**2**), which can be derived from styrene. By the treatment of styrene in dichloromethane with sodium nitrite and acetic acid, 4-nitro-3-phenylfurazan 2-oxide (**1**) was obtained in one step in 68% yield. We have found that the nitro group of **1** can be replaced easily with azide ion. The azide **2** was thus obtained in nearly quantitative yields by the treatment of **1** with sodium azide in dimethyl sulfoxide for 10 min.

We have expected that the structure of **2** is favorable to the formation of the oxime having the *E* configuration. Namely, the decomposition of azide **2** may produce a nitrene intermediate, which will be converted to oxime **3a** by subsequent ring cleavage and elimination of an NO segment in a manner shown in Scheme 1. On the base of this idea, we examined decomposition of the azide under various conditions.



Scheme 1.

We first tried to pyrolyze the azide **2** in refluxing xylene. The reaction occurred, however, only very slowly and yields of the oximes were low (totally 13%). The decomposition rate and the yield were improved markedly by addition of alcohols. Alcohols may promote the elimination of the NO segment by forming a nitrite ester. In refluxing 1-pentanol, the reaction completed within 3 h and a mixture of (*E*)-oxime, mp

100 °C, and (*Z*)-oxime, mp 130 °C, was obtained (15% and 30% yields, respectively).[6]

When photolysis was applied, a dramatic improvement in both conversion and stereoselectivity was realized. By irradiation with UV light longer than 300 nm in the presence of alcohols, the azide decomposed quite smoothly and cleanly. The reaction completed within 25 min, leading to the selective formation of the *E*-isomer in 94% yield.[7]

Although the photolysis of **2** proves to be quite effective to obtain (*E*)-oxime, the route needs three-step reactions from styrene. We hence tried to shorten the reaction steps and found that the conversion can be performed successively without isolation of any intermediates. Namely, when styrene was treated in the manner as described in the experimental section, the oxime **3a** was obtained conveniently in 60% overall yield.

As described above, our route to the (*E*)-oxime starts from styrene and the whole process is very simple. The oxime will be utilized further as a synthetic intermediate, providing a new synthetic entry.[8]

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References

1) M. Ito, D. Hagiwara, and T. Kamiya, *Tetrahedron Lett.*, **1975**, 4393.
2) H. Wieland, *Ann. Chem.*, **328**, 154 (1903).
3) O. Touster, *Org. React.*, **7**, 327 (1953).
4) T. E. Stevens, *J. Org. Chem.*, **32**, 670 (1966).
5) Stevens has tried to isolate the (*E*)-oxime by chromatography, but the yield was only several percents (Ref. 4).
6) Both isomers were characterized in comparison with Steven's results (Ref. 4). His *syn*-compound corresponds to our *E*-compound and *anti*- to *Z*-, respectively.
7) Prolonged exposure to UV light or unnecessary heating should be avoided, since the (*E*)-oxime changes gradually into the *Z*- form under these conditions.
8) We have already found that 2-phenylglycine is obtained in good yields by electrochemical reduction of the oxime.