Gold(III)-Catalyzed One-Pot Synthesis of Isoxazoles from Terminal Alkynes and Nitric Acid

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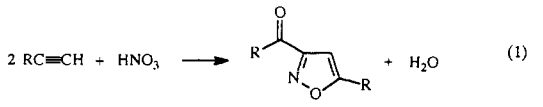
A challenging goal in organic chemistry is to link together in one reaction flask three or more components *via* sequential bond-forming processes. Success would provide rapid and efficient means for transforming simpler molecules into more complex, nonpolymeric, useful compounds. In this paper we describe a one-flask multicomponent reaction of a hitherto unknown (2 + 2 + 1) type leading to the formation of 3,5-disubstituted isoxazoles.

Isoxazoles play interesting roles in medicinal and agricultural chemistry,[1] and moreover they are precursors of several functional groups by ring modification and cleavage.[2,3]

There are, however, some limitations to the structural variety of isoxazoles readily available.[3] They are generally prepared by reaction of 1,3-dicarbonyl compounds with hydroxylamine followed by dehydrative cyclization of the intermediate monoxime. In the case of unsymmetrical 1,3-diketones, however, this reaction leads to the formation of a mixture of isomers.[4] Another route to the formation of isoxazoles is the 1,3-dipolar cycloaddition of nitrile oxides to acetylenes.[5] However, only the aromatic nitrile oxides are readily available, while the nonaromatic ones are unstable and dimerize to furoxanes; furthermore, the more common precursors of nitrile oxides, the hydroximoyl chlorides, are severe skin irritants.

The two routes outlined above [both of the type (3 + 2) according to the number of isoxazole ring atoms in each component synthon] cover ca. 90% of the isoxazole preparations. Other routes of the types (4 + 1), (5 + 0), and (3 + 1 + 1) provide the syntheses of some specific isoxazoles and are of rather limited utility.[5]

We find that terminal alkynes[6] react smoothly with nitric acid under biphasic conditions (nitromethane/water, 1:1 v/v)[7] and in the presence of a catalytic amount of tetrabutylammonium tetrachloroaurate ($TBA^+AuCl_4^-$) to give 3,5-disubstituted isoxazoles according to eq 1 (Table I).



(1)

There are no apparent limitations to the nature of R, and in the several cases we have examined (R = Ph, *n*-Pr, *n*-Bu, $BzOC_2H_4$), the yield of the isolated 3,5-disubstituted isoxazole was in the range 35–50%.[8]

During the reaction, most of the gold is present in the reduced form, $AuCl_2^-$, indicating that the gold(III) takes part in the redox process, and the rate of reduction by the alkyne is faster than its reoxidation by nitric acid. Reduction products of nitric acid were detected in the solution (NO_2^-) and in the gas phase (traces of NO and NO_2). The reaction rate is increased by addition of a moderate amount of NO_2^- ($NaNO_2$) to the reaction system.

The formation of isoxazole takes place in this biphasic system also in the absence of the $TBA^+AuCl_4^-$ catalyst (pathway b in Scheme I), but the reaction rate and the yield of product are smaller (yield less than 6% after 5 h). Furthermore, poor results are obtained by using a different metal catalyst (e.g., $PdCl_4^{2-}$, $CuCl_4^{2-}$, $HgCl_4^{2-}$, always as TBA^+ salts). The yields are less than 10% after a reaction time of 7–20 h.

Most probably, the simultaneous attack on the triple bond of an electrophile ($AuCl_3$ in pathway a and H^+ in pathway b) and of a nucleophile (NO_2^-) causes the formation of a vinyl nitrite (**Ia** and **Ib**, respectively). **Ia** can rearrange to the nitrile oxide **III** via $AuCl_2^-$ and HCl elimination, whereas **Ib** can first isomerize to the acyloxime **IIb**[9] and then be oxidized to the nitrile oxide **III** by nitric acid. The formation of a nitrile oxide as an intermediate was proven by performing an experiment in which an excess of alkene (10 times the amount of alkyne) was added to the reaction

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(3) Lang, S. A., Jr.; Lin, Y. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. 6, pp 1–130. Quilico, A. In *Five- and Six-Membered Compounds with Oxygen and Nitrogen*; Wiley, R. H., Ed., Wiley-Interscience: New York, 1962; pp 1–46. Rochetkov, N. K. L.; Dokolov, E. D. *Adv. Heterocycl. Chem.* **1963**, *2*, 365. Wakefield, B. J.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 147. Nisniwaki, T. *Synthesis* **1975**, 20. Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*; Martin, F. A., Ed.; Elsevier Science Pub. B.V.: Amsterdam, 1986; Vol. IVC, pp 243–283. Kashima, C. *Heterocycles* **1979**, *12*, 1343. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. Grünanger, P.; Vita-Finzi, P. Isoxazoles. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley Interscience: New York, 1991; Vol. 49, Part I, pp 125–416.

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(5) Quilico, A.; Speroni, G. *Gazz. Chim. Ital.* **1946**, *76*, 148. Quilico, A.; Simonetta, M. *Gazz. Chim. Ital.* **1946**, *76*, 200. Quilico, A.; Stagno D'Alcontres, G. *Gazz. Chim. Ital.* **1949**, *79*, 654. Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3258. Christl, M.; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3275. Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291. Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403. Grundmann, C.; Kite, G. F. *Synthesis* **1973**, 156. Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 1, p 291.

(6) The reaction of acetylene gas with fuming nitric acid was reported (Baschieri, A. *Gazz. Chim. Ital.* **1901**, *31*, 461. Testoni, G.; Mascarelli, L. *Gazz. Chim. Ital.* **1902**, *32*, 202. Mascarelli, L. *Gazz. Chim. Ital.* **1903**, *33*, 319), and later it was shown to give a mixture of isoxazole derivatives bearing oxygen-containing substituents in the 3 position (Quilico, A.; Freri, M. *Gazz. Chim. Ital.* **1929**, *59*, 930; **1930**, *60*, 172, 721; **1931**, *61*, 484. Quilico, A. *Gazz. Chim. Ital.* **1931**, *61*, 265, 759, 970; **1932**, *62*, 503). This reaction, however, is not of practical utility because of the strong oxidative conditions and of the poor miscibility of the alkynes with nitric acid.

(7) A similar biphasic system has been employed for the selective oxidation of sulfides to the corresponding sulfoxides (Gasparrini, F.; Giovannoli, M.; Misiti, D.; Natile, G.; Palmieri, G. *Tetrahedron* **1983**, *39*, 3181; **1984**, *40*, 165; *Synth. Commun.* **1988**, *18*, 69; *J. Org. Chem.* **1990**, *55*, 1323).

(8) In a typical experiment, the alkyne (5.0 mmol) was dissolved in nitromethane (8 mL) and treated with aqueous HNO_3 (16 mL, 25.0 mmol, 1.56 M) in the presence of tetrabutylammonium tetrachloroaurate(III) (0.25 mmol) and sodium nitrite (1.0 mmol). The mixture was stirred at 50 °C until complete disappearance of the alkyne and then was extracted with dichloromethane. The extract was washed with a saturated aqueous solution of $Na_2S_2O_3$ which removed the catalyst and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was chromatographed on an open column of silica gel using ethyl acetate/cyclohexane as eluant. The yield of the pure isolated product was between 35% and 50%. Elemental analyses, molecular weight (mass spectra), and ^1H and ^{13}C NMR data were in accord with the given formulation.

(9) Boyer, J. H. Methods of Formation of the Nitroso Group and Its Reactions. In *The Chemistry of the Nitro and Nitroso Groups*; Patai, S., Feuer, H., Eds.; Wiley Interscience: New York, 1969; Part 1, pp 220–222, and refs therein.

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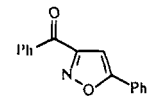
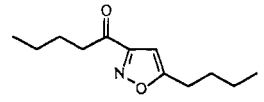
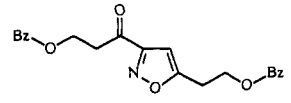
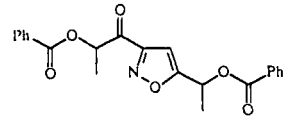
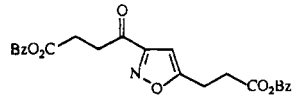
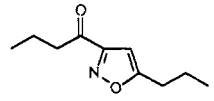
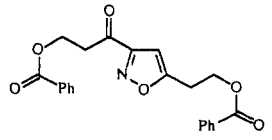
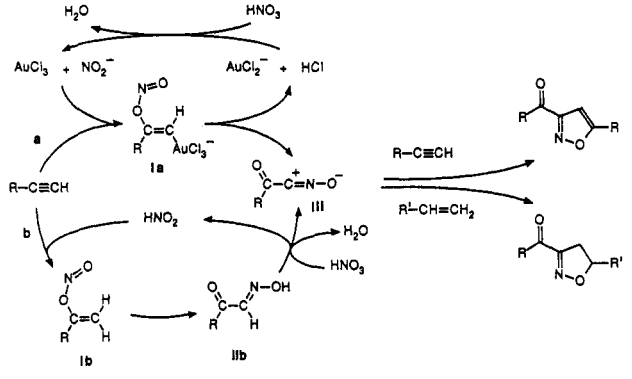
Table I. Yields of the Isolated 3,5-Disubstituted Isoxazoles[8]

substrate	product	reaction time (h)	yield (%)
PhC≡CH (**1a**)	**2a** 	5	40
$CH_3(CH_2)_3C{\equiv}CH$ (**1b**)	**2b** 	1	38
$BzOCH_2CH_2C{\equiv}CH$ (**1c**)	**2c** 	5	37
$CH_3CH(OCOPh)C{\equiv}CH$ (**1d**)	**2d** 	5	37
$BzO_2CCH_2CH_2C{\equiv}CH$ (**1e**)	**2e** 	4	50
$CH_3CH_2CH_2C{\equiv}CH$ (**1f**)	**2f** 	1	35
$PhCOOCH_2CH_2C{\equiv}CH$ (**1g**)	**2g** 	1	43

Scheme I



system as a nitrile oxide scavenger.[10] In this case, the corresponding isoxazoline, resulting from 1,3-dipolar cycloaddition of the alkene to **III**, was the major product.[11,12] In general, a small amount of the ketone derived from the terminal alkyne ($RCOCH_3$) was found in the reaction mixture. We proved that the ketone is a byproduct and not a reaction intermediate by performing an experiment in which a preformed ketone (acetophenone) was added to the reaction system. Starting with 1-hexyne, only the isoxazole **2b** was formed, while the acetophenone was recovered unchanged.

The biphasic system of nitromethane/water proved to be unique in promoting this type of reaction, and this could explain why such a reaction has not been reported previously.

The main characteristics of this approach to the synthesis of 3,5-disubstituted isoxazoles may be identified in the originality of the (2 + 2 + 1) reaction type and in the same starting material being both the precursor of the nitrile oxide generated in situ and the reagent for the subsequent 1,3-dipolar cycloaddition.

Supplementary Material Available: Tables of characterization data for newly prepared alkynes (S-I) and isoxazoles (S-II) (3 pages). Ordering information is given on any current masthead page.

(10) The reaction was performed as described in ref 8 but starting with a mixture of phenylacetylene (5 mmol) and 1-hexene (50 mmol) instead of pure alkyne (5 mmol). 3-Benzoyl-5-butylisoxazoline was obtained in 40% yield. The elemental analysis, molecular weight (mass spectrum), and ^1H and ^{13}C NMR data were in accord with the given formulation.

(11) Quilico, A.; Stagno d'Alcontres, G.; Grünanger, P. *Nature* **1950**, *166*, 226.

(12) The regioselectivity of the 1,3-dipolar cycloaddition has been proved by spectroscopic experiments (NMR, DEPT) and, in addition, by comparison of the compound **2a** with an authenticated sample.[13] The assignment of all sp^2 carbons of the isoxazolic cycle and of the side carbonyl group was not possible taking into account only their chemical shifts. This problem was overcome by running the INADEQUATE[14] experiment on the sp^2 region of the ^{13}C spectrum of the model compound 3-pentanoyl-5-butylisoxazole (**2b**). An accurate evaluation of the coupling constants of the satellites of the four ^{13}C resonances allowed their unambiguous assignments.

(13) Nelson, S. D., Jr.; Kasparian, D. J.; Trager, W. F. *J. Org. Chem.* **1972**, *37*, 2686.

(14) Bax, A.; Freeman, R.; Kempsell, S. P. *J. Am. Chem. Soc.* **1980**, *102*, 4851.