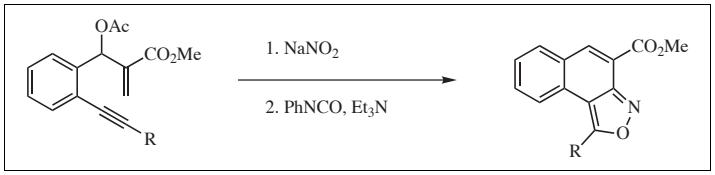
The Dipolar Route to Naphtho[2,1-*c*]isoxazoles from the Baylis-Hillman Adducts of 2-Alkynylbenzaldehydes

Sang-Hoon Ji, Wan Pyo Hong, Seung Ho Ko and Kee-Jung Lee*

Organic Synthesis Laboratory, Department of Chemical Engineering,
Hanyang University, Seoul 133-791, Korea

Received August 20, 2005



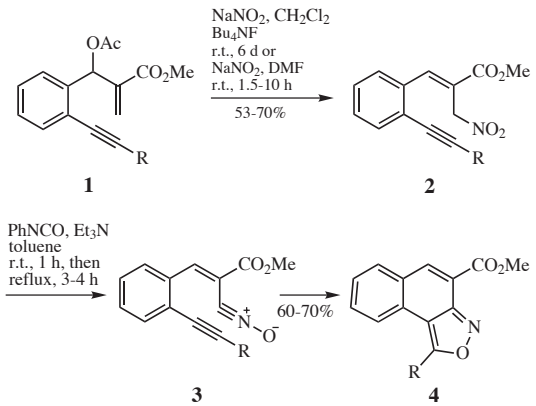
A new synthesis of 4-carbomethoxynaphtho[2,1-*c*]isoxazoles **4a**-**d** from methyl 3-(alkynylphenyl)-2-nitromethyl-2-propenoates **2a**-**d** by the intramolecular nitrile oxide cycloaddition is described. The latter are readily obtained from 2-alkynylbenzaldehydes through the Baylis-Hillman adduct acetates **1a**-**d** followed by nucleophilic substitution of nitrite anion.

J. Heterocyclic Chem., **43**, 799 (2006).

Many industrial uses of isoxazoles and their benzo-fused analogues have been reported [1]. Pharmacologically-useful isoxazoles [2] include the antibiotic sulfisoxazoles, oxacillin, cloxacillin and dichloxacillin, an antileprous compound, the monoamine oxidase inhibitor, isocarboxazid [3], the central nervous system active isoxazole agarin [4], and the important isoxazole derivative cycloserine, an antituberculosis drug [3]. Isoxazoles have also been used extensively as synthetic equivalents of β-dicarbonyls and α-cyanoketones [5], and transformed into a wide range of other heterocycles [6]. Therefore, it is important to develop new and more efficient synthetic pathways to a diverse array of isoxazole pharmacophores. Two main routes exist in involving condensation reactions of 1,3-dicarbonyl compounds with hydroxylamines [7] and 1,3-dipolar cycloaddition of nitrile oxides to alkynes [8], although there are many variations within these types and several other synthetic methods are available.

The Baylis-Hillman reaction has been the subject of recent reviews [9] and continues to elicit attention. We and other groups have demonstrated applications of this reaction in the synthesis of benzannulated or other heterocyclic systems. These include indolizines [10], quinolines [11], chromenes [12], thiochromenes [13], indenes [14], pyridopyrimidones [15], 1,4-oxazepin-7-ones [16], coumarins [17], isobenzofurans [18], 3-oxo-2,3-dihydro-1*H*-isoindoles [19], 1*H*-indoles [20], and 2-benzazepines [21]. Also, we described facile syntheses of 4*H*-tetrazolo[1,5-*a*][1]benzazepines [22] and 5*H*-1,2,3-triazolo[4,3-*a*][2]benzazepines [23] from the Baylis-Hillman adducts of 2-azidobenzaldehyde and 2-alkynylbenzaldehydes using intramolecular 1,3-dipolar cycloaddition reaction, respectively. We herein report a new synthesis of naphtho[2,1-*c*]isoxazoles *via* the treatment of the acetates of Baylis-Hillman adduct of 2-alkylnylbenzaldehydes with nitrite anion and subsequent *in situ* generation of nitrile oxides by the dehydration of 2-nitromethylcinnamates with phenyl isocyanate-triethylamine [24] followed by intramolecular 1,3-dipolar cycloaddition reaction.

Scheme I



1, **2**, **3**, **4**	R
a	H
b	Ph
c	Bu
d	CH_2OMe

The readily available *o*-acetylenic Baylis-Hillman adduct acetates **1a**-**d**, whose preparation has been previously described [23], provided a convenient starting point for the synthesis of this ring system, as shown in Scheme I. Treatment of Baylis-Hillman acetates **1a**-**d** with sodium nitrite in *N,N*-dimethylformamide at room temperature for 1.5-10 hours afforded *o*-acetylenic 2-nitromethylcinnamic acid methyl esters **2a**-**d** in 20-70% yields [17b]. A better

result was obtained when **1a** in dichloromethane was treated with sodium nitrite in the presence of tetrabutylammonium fluoride hydrate at room temperature for 6 days, thus providing **2a** in 53% yield. The (*E*)-stereochemistry of the products was established by comparing ^{1}H nmr values of olefinic and methylene protons with literature values [17b]. *In situ* generation of nitrile oxides by the dehydration of 2-nitromethylcinnamic acid methyl esters **2a**-**d** with phenyl isocyanate in the presence of catalytic amounts of triethylamine, and subsequent intramolecular 1,3-dipolar cycloaddition reaction of nitrile oxides **3a**-**d** to triple bonds in refluxing toluene produced in moderate yields (60-70%) of the corresponding 4-carbomethoxynaphtho[2,1-*c*]isoxazoles **4a**-**d**. In the ^{1}H nmr spectra of **4a**-**d**, the characteristic chemical shift of the methine proton of C5 were found at δ = 8.44-8.47, and methyl protons of esters were observed at δ = 4.06-4.09 as singlets. The ^{13}C nmr values are in good agreement with those reported for a similar system [25].

In conclusion, we have developed a new strategy involving an intramolecular 1,3-dipolar cycloaddition of nitrile oxides to alkynes leading to the synthesis of naphtho[2,1-*c*]isoxazole derivatives, only limited numbers of reports were known [26], from the Baylis-Hillman adducts.

EXPERIMENTAL

All reagents and solvents were reagent grade or were purified by standard methods before use. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (tlc) was performed on silica gel with fluorescent indicator coated on aluminum sheets. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba EA 1180 element analyzer. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^{1}H and ^{13}C nmr spectra were measured on a Gemini 300 spectrometer using deuteriochloroform. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane.

The methyl 3-acetoxy-3-(2-ethynylphenyl)-2-methylenepropanoate (**1a**), methyl 3-acetoxy-2-methylene-3-[(2-phenylethynyl)phenyl]propanoate (**1b**), methyl 3-acetoxy-3-[2-(1-hexyn-1-yl)phenyl]-2-methylenepropanoate (**1c**) and methyl 3-acetoxy-3-[2-(3-methoxypropyn-1-yl)phenyl]-2-methylenepropanoate (**1d**) were prepared following the literature procedure [23].

Methyl 3-(2-Ethynylphenyl)-2-nitromethyl-2-propenoate (**2a**).

To a stirred solution of 1.03 g (4 mmoles) of **1a** in 20 ml of dichloromethane was added 0.41 g (6 mmoles) of sodium nitrite and 0.21 g (0.8 mmoles) of tetrabutylammonium fluoride hydrate at room temperature. After stirring at the same temperature for 6 days the reaction mixture was diluted with 10 ml of water and extracted with diethyl ether (5 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (15:1) to afford 0.52 g (53%) of **2a** as a solid after crystallization with hexane; mp 93-94 °C; ir (potassium bromide): 3283, 1712, 1641, 1555, 1389, 1357, 1300 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.39 (s, 1 H), 3.89 (s, 3 H), 5.27 (s, 2 H), 7.26-7.29 (m, 1 H), 7.38-7.44 (m, 2 H), 7.58-7.61 (m, 1 H), 8.37 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 52.8, 71.9, 80.7, 83.7, 122.5, 123.3, 127.8, 128.2, 129.4, 133.4, 135.9, 145.9, 165.8.

Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.41; H, 4.30; N, 5.52.

Methyl 2-Nitromethyl-3-[(2-phenylethynyl)phenyl]-2-propenoate (**2b**).

To a stirred solution of 1.33 g (4 mmoles) of **1b** in 20 ml of *N,N*-dimethylformamide was added 0.41 g (6 mmoles) of sodium nitrite at room temperature. After stirring at the same temperature for 1.5 hours the reaction mixture was diluted with 10 ml of water and extracted with diethyl ether (5 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (4:1) to afford 0.90 g (70%) of **2b** as a solid after crystallization with diethyl ether and petroleum ether; mp 94-96 °C; ir (potassium bromide): 1712, 1631, 1555, 1493, 1385, 1353 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.89 (s, 3 H), 5.32 (s, 2 H), 7.31-7.64 (m, 9 H), 8.52 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 52.7, 71.9, 86.6, 96.2, 122.5, 122.9, 123.8, 128.0, 128.5, 129.8, 131.5, 131.7, 132.4, 132.6, 135.3, 146.4, 165.9.

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 69.91; H, 4.64; N, 4.22.

Methyl 3-[2-(1-Hexyn-1-yl)phenyl]-2-nitromethyl-2-propenoate (**2c**).

The procedure was the same as described in the preparation of **2b** with **1c** (1.26 g, 4 mmoles) except reaction time (10 hours). Yield: 0.71 g (59%); oil; ir (neat): 2226, 1714, 1642, 1555, 1435, 1385, 1355 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.95 (t, 3 H, J = 7.32 Hz), 1.48 (m, 2 H), 1.58 (m, 2 H), 2.45 (t, 2 H, J = 7.02 Hz), 3.88 (s, 3 H), 5.28 (s, 2 H), 7.21-7.23 (m, 1 H), 7.29-7.38 (m, 2 H), 7.46-7.50 (m, 1 H), 8.38 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 13.5, 19.2, 21.9, 30.6, 52.6, 72.0, 78.1, 97.7, 122.5, 124.7, 127.8 (two peaks), 129.7, 132.7, 135.3, 146.8, 166.0.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.59; H, 6.48; N, 4.39.

Methyl 3-[2-(3-Methoxypropyn-1-yl)phenyl]-2-nitromethyl-2-propenoate (**2d**).

The procedure was the same as described in the preparation of **2b** with **1d** (1.21 g, 4 mmoles). Yield: 0.66 g (57%); oil; ir (neat): 1717, 1630, 1555, 1431, 1388 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.45 (s, 3 H), 3.87 (s, 3 H), 4.35 (s, 2 H), 5.28 (s, 2 H), 7.25-7.57 (m, 4 H), 8.37 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 52.7, 57.6, 60.3, 71.8, 83.6, 91.7, 123.1 (two peaks), 127.9, 128.8, 129.8, 132.9, 135.4, 146.2, 165.9.

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.21; H, 5.13; N, 4.63.

4-Carbomethoxynaphtho[2,1-*c*]isoxazole (**4a**).

To a stirred solution of 0.49 g (2 mmoles) of **2a** in 10 ml of dry toluene, containing a few drops of triethylamine, was added 0.52 g (4.4 mmoles) of phenyl isocyanate. The solution was allowed to stand at room temperature for 1 hour and at reflux temperature for 3 hours. Diphenylurea was filtered, toluene was removed *in vacuo*, and the residue was chromatographed on silica gel eluting with hexane/ethyl acetate (8:1) to yield 0.30 g (65%) of **4a** as a solid after crystallization with dichloromethane and diethyl ether; mp 156 °C; ir (potassium bromide): 1697, 1629, 1548, 1433, 1317 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.07 (s, 3 H), 7.54-8.07 (m, 4 H), 8.47 (s, 1 H), 9.41 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 52.7, 117.3, 117.5, 124.5, 127.3, 127.6, 129.4, 130.9, 131.0, 140.3, 152.9, 153.4, 165.0.

Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.50; H, 3.78; N, 5.98.

4-Carbomethoxy-1-phenylnaphtho[2,1-*c*]isoxazole (**4b**).

The procedure was the same as described in the preparation of **4a** with **2b** (0.64 g, 2 mmoles). Yield: 0.36 g (60%); mp 182-183 °C; ir (potassium bromide): 1702, 1624, 1551, 1432, 1312 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.09 (s, 3 H), 7.48-8.18 (m, 9 H), 8.47 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 52.6, 112.1, 117.6, 123.0, 123.1, 127.4, 128.2, 128.7, 129.0, 129.6, 130.4, 130.8, 131.2, 140.5, 154.4, 165.1, 166.3.

Anal. Calcd for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.03; H, 4.10; N, 4.45.

1-Butyl-4-carbomethoxynaphtho[2,1-*c*]isoxazole (**4c**).

The procedure was the same as described in the preparation of **4a** with **2c** (0.60 g, 2 mmoles) except eluent [dichloromethane/ methanol (30:1)]. Yield: 0.40 g (70%); mp 58-59 °C; ir (potassium bromide): 1697, 1629, 1549, 1433, 1317 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.99 (t, 3 H, J = 7.32 Hz), 1.50 (sextet, 2 H, J = 7.32 Hz), 1.92 (quintet, 2 H, J = 7.63 Hz), 3.40 (t, 2 H, J = 7.63 Hz), 4.06 (s, 3 H), 7.51-8.09 (m, 4 H), 8.44 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 13.6, 22.3, 28.0, 29.0, 52.6, 111.6, 117.6, 123.2, 126.6, 128.8, 129.3, 130.7, 131.2, 140.3, 154.0, 165.2, 169.6.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 69.85; H, 5.98; N, 4.76.

4-Carbomethoxy-1-methoxymethylnaphtho[2,1-*c*]isoxazole (**4d**).

The procedure was the same as described in the preparation of **4a** with **2d** (0.58 g, 2 mmoles) except reaction time (4 hours). Yield: 0.36 g (67%); mp 87-88 °C; ir (potassium bromide): 1711, 1634, 1550, 1440, 1309 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.44 (s, 3 H), 4.07 (s, 3 H), 5.11 (s, 2 H), 7.55-8.28 (m, 4 H), 8.47 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 52.6, 58.5, 65.1, 114.4, 117.6, 125.4, 127.4, 127.8, 129.6, 131.0 (two peaks), 140.6, 154.4, 164.6, 165.0.

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.20; H, 4.71; N, 5.02.

Acknowledgement.

This research was supported by University IT Research Center Project.

REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

[1] K. -H. Wunsch and A. J. Boulton, *Adv. Heterocycl. Chem*., **8**, 277 (1967).

[2] C. O. Wilson, O. Gisvold and R. F. Doerge, In Textbook of Medicinal and Pharmaceutical Chemistry; Pitman, London, 1966.

[3] N. K. Kochetkov and S. D. Sokolov, *Adv. Heterocycl. Chem*., **2**, 365 (1963).

[4] B. Loev, *J. Med. Chem*., **13**, 738 (1970).

[5] A. I. Meyers, In Heterocycles in Organic Synthesis; Wiley-Interscience, New York, 1974.

[6a] A. Boulton, A. R. Katritzky and A. Majid Hamid, *J. Chem. Soc. (C)*, 2005 (1967); [b] T. Nishiwaki, *Synthesis*, 20 (1975).

[7a] Reviews on isoxazoles: A. Quilico, In Isoxazoles and Related Compounds, ed. A. Weissberger, *The Chemistry of Heterocyclic Compounds*, Vol. **17**, Interscience, New York, 1962, pp 1-176; [b] B. J. Wakefield and D. J. Wright, *Adv. Heterocycl. Chem*., **25**, 147 (1979); [c] S. D. Sokolov, *Usp. Khim*., **48**, 533 (1979); [d] C. Kashima, *Heterocycles*, **12**, 1343 (1979).

[8a] R. Huisgen, *Angew. Chem. Int. Ed. Engl*., **2**, 565 (1963); [b] R. Huisgen, *Angew. Chem. Int. Ed. Engl*., **2**, 633 (1963).

[9a] S. E. Drewes and G. H. P. Roos, *Tetrahedron*, **44**, 4653 (1988); [b] D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, **52**, 8001 (1996); [c] J. N. Kim and K. Y. Lee, *Curr. Org. Chem*., **6**, 627 (2002); [d] D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev*., **103**, 811 (2003); [e] E. Ciganek, In Organic Reactions, ed. L. A. Paquette; Wiley, New York, 1997, Vol. **51**, pp 201-350.

[10] M. L. Bode and P. T. Kaye, *J. Chem. Soc., Perkin Trans. 1*, 2612 (1990); [b] M. L. Bode and P. T. Kaye, *J. Chem. Soc., Perkin Trans. 1*, 1809 (1993).

[11a] O. B. Familoni, P. T. Kaye and P. J. Klaas, *Chem. Commun*., 2563 (1998); [b] J. N. Kim, K. Y. Lee, H. S. Kim and T. Y. Kim, *Org. Lett*., **2**, 343 (2000); [c] J. N. Kim, H. J. Lee, K. Y. Lee and H. S. Kim, *Tetrahedron Lett*., **42**, 3737 (2001); [d] J. N. Kim, H. S. Kim, J. H. Gong and Y. M. Chung, *Tetrahedron Lett*., **42**, 8341 (2001).

[12] P. T. Kaye and X. W. Nocanda, *J. Chem. Soc., Perkin Trans. 1*, 1331 (2000).

[13] P. T. Kaye and X. W. Nocanda, *Synthesis*, 2389 (2001).

[14] D. Basavaiah, M. Bakthadoss and G. J. Reddy, *Synthesis*, 919 (2001).

[15] D. Basavaiah and T. Satyanarayana, *Tetrahedron Lett*., **43**, 4301 (2002).

[16] R. Rächer, K. Döring, and O. Reiser, *J. Org. Chem*., **65**, 6932 (2000).

[17a] P. T. Kaye, M. A. Musa and X. W. Nocanda, *Synthesis*, 531 (2003); [b] W. P. Hong and K. -J. Lee, *Synthesis*, 33 (2005).

[18] V. Nair and K. G. Abhilash, *Synthesis*, 1967 (2005).

[19] Y. S. Song, C. H. Lee and K. -J. Lee, *J. Heterocyclic Chem*., **40**, 939 (2003).

[20] C. R. Horn and M. Perez, *Synlett* 1480 (2005).

[21] D. Basavaiah and T. Satyanarayana, *Chem. Commun*., 32 (2004).

[22] C. H. Lee, Y. S. Song, H. I. Cho, J. W. Yang and K. -J. Lee, *J. Heterocyclic Chem*., **40**, 1103 (2003).

[23] S. H. Ko and K. -J. Lee, *J. Heterocyclic Chem*., **41**, 613 (2004).

[24] T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc*., **82**, 5339 (1960).

[25] T. R. Kasturi, J. A. Sattigeri and P. V. P. Pragnacharyulu, *Tetrahedron* **51**, 3051 (1995).

[26a] A. P. Kozikowski and Y. -Y. Chen, *J. Org. Chem*., **46**, 5250 (1981); [b] A. P. Kozikowski and P. D. Stein, *J. Am. Chem. Soc*., **107**, 2569 (1985).