Faramarz Rostami-Charati,[a]* Zinatossadat Hossaini,[b] Ebrahim Gharaee,[b] and Mohammad A. Khalilzadeh[b]

[a]Department of Chemistry, Faculty of Science, Gonbad Kavous University, P.O. Box 163, Gonbad, Iran
[b]Department of Chemistry, Qaemshahr Branch, Islamic Azad University, Qaemshahr, Iran
*E-mail: f_rostami_ch@yahoo.com

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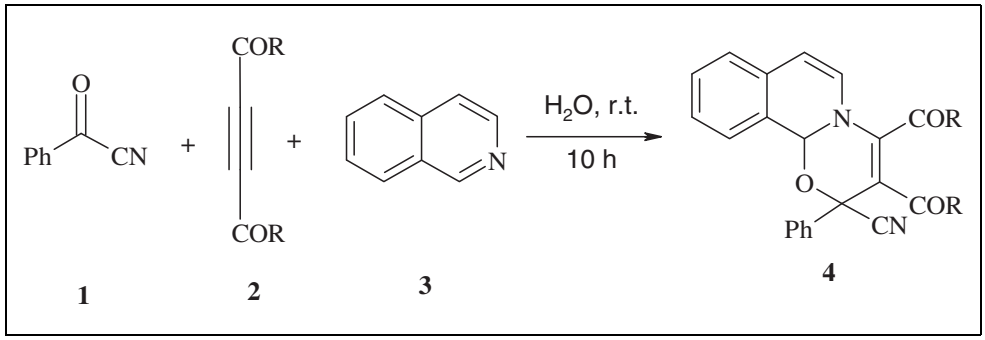

A one-pot synthesis of oxazine derivatives via reaction between activated acetylenic compounds, benzoyl cyanide, and *N*-nucleophiles in water as the solvent is described.

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INTRODUCTION

Water is an ideal solvent and reagent for biochemical transformations. In the past, water was not used as a solvent for synthetic organic chemistry owing to the poor solubility and, in some cases, the instability of organic reagents in aqueous solutions. Now, it has been recognized that chemical reactions in mixed aqueous solutions or two-phase systems often give better results than in organic solvents, and often the insolubility of the final products facilitates their isolation [1–4].

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity [5]. As part of our current studies on the development of new routes in heterocyclic synthesis, we report an efficient procedure for direct synthesis of oxazine derivatives **4** from the reaction of benzoyl cyanide **1** and activated acetylenic compounds **2** in the presence of *N*-nucleophiles such as isoquinoline, quinolin, or *N*-methylimidazole **3** in water at room temperature (Scheme 1).

RESULT AND DISCUSSION

The structures of compounds **4a–4d** were apparent from their ^{1}H NMR and ^{13}C NMR spectroscopic data, as well as infrared (IR) spectra, in agreement with the proposed structures. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ exhibited two singlets for the methoxy protons (δ 3.59 and 4.03 ppm) and one singlet for the methin (δ 6.57 ppm) proton along with multiplets for the aromatic moiety. The ^{13}C NMR spectrum of **4a** exhibited 21 signals in agreement with the proposed structure.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the reaction involves the initial formation of a 1:1 zwitterionic intermediate [6] **5** between isoquinoline and the activated acetylene, which undergoes reaction with **1** to produce **6**. Intermediate **6** can undergo cyclization under the reaction conditions employed to produce **4** (Scheme 2).

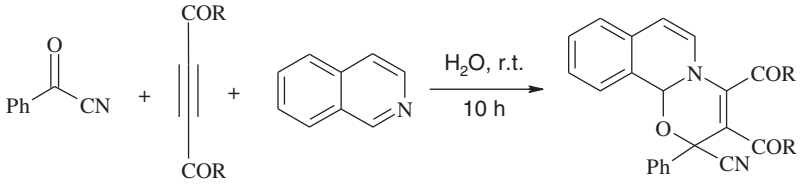
Under similar conditions, the reaction of quinoline, pyridine, or *N*-methylimidazole with dialkyl acetylenedicarboxylates in the presence of **1** led to fused [1,3]oxazines **7–9** in good yields (Scheme 3).

In conclusion, we report a novel transformation involving activated acetylenes and isoquinoline, quinoline, or pyridine in the presence of benzoyl cyanide, which affords bridgehead nitrogen-containing heterocycles. The present procedure has the advantage that not only is the reaction performed in water but also the reactants can be mixed without any prior activation or modification. The simplicity of the present procedure makes it an interesting alternative to other approaches.

EXPERIMENTAL

All chemicals were obtained from commercial sources. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer (Bruker, Germany) in chloroform-d1, and tetramethylsilane was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer

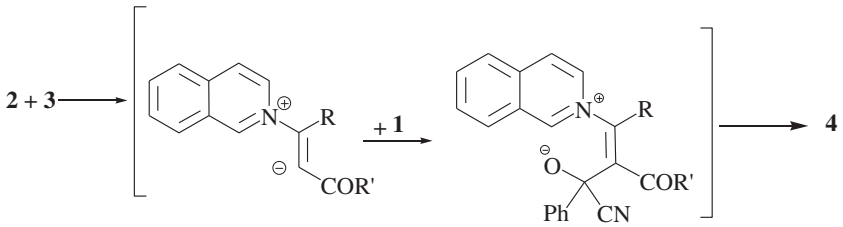
Scheme 1. Three-component reactions of benzoyl cyanide, activated acetylenes, and isoquinoline.



1 **2** **3** **4**

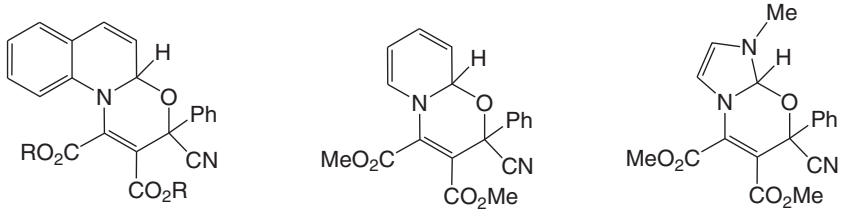
2, 4	R	Yield (%) of **4**
a	MeO	90
b	EtO	72
c	^{t}BuO	75
d	Ph	82

Scheme 2. Proposed mechanism for the one-pot synthesis of [1, 3]oxazines.



5 **6**

Scheme 3. Three-component reactions of benzoyl cyanide, activated acetylenes and quinoline, pyridine, and *N*-methylimidazole.



7	R	Yield/ %
a	Me	75
b	Et	72

8 (76%) **9** (82%)

(Vernon Hills, IL). IR spectra were acquired on a Nicolet Magna 550-FT spectrometer (Oshawa, Ontario, Canada). Elemental analyses were carried out with a PerkinElmer model 240-C apparatus (England). The results of elemental analyses (C, H, and N) were within ±0.4% of the calculated values.

General procedure for preparation of compounds 4a–4d and 7–9. Magnetically stirred solution of benzoyl cyanide (2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) in H_2O (10 mL) was added isoquinoline, quinoline, pyridine, or *N*-methylimidazole (2 mmol), and the reaction was mixed for 10 h at room temperature. The completion of reaction was confirmed by TLC (EtOAc–hexane 6:1). The resulting precipitate was separated by filtration and recrystallized from EtOH to afford the pure title compounds.

Dimethyl 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino [2,3-a]isoquinoline-3,4-dicarboxylate (4a). Yellow powder, mp 68–70°C, 0.36 g, yield 90%. IR (KBr) (ν_{max}/cm^{-1}): 1737 (C═O), 1699 (C═O), 1582, 1556, 1420, 1277, 1232. MS (EI, 70 eV): *m/z* (%) = 401 (2), 149 (64), 129 (44), 105 (90), 77 (100), 59 (86). *Anal.* Calcd for $C_{23}H_{18}N_2O_5$ (402.40): C, 68.65 H, 4.51 N, 6.96%. Found: C, 68.71 H, 4.60 N, 7.07%. ^{1}H NMR: δ 3.59 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 5.88 (d, ^3J = 7.8, 1H, CH), 6.40 (d, ^3J = 7.8, 1H, CH), 6.57 (s, 1H, CH), 7.13 (d, ^3J = 7.5, 1H, CH), 7.29 (t, ^3J = 7.1, 1H, CH), 7.34 (d, ^3J = 7.4, 1H, CH),

7.38–7.40 (m, 3 H, 3 CH), 7.48 (d, ^3J = 7.7, 1H, CH), 7.65–7.67 (m, 2 H, 2 CH). ^{13}C NMR: δ 51.9 (OCH_3), 53.7 (OCH_3), 78.1 (C), 82.1 (CH), 106.1 (CH), 118.1 (CN), 122.8 (CH), 125.1 (C), 125.5 (CH), 126.6 (2 CH), 127.7 (CH), 128.1 (CH), 128.7 (2 CH), 128.9 (C), 129.4 (C), 129.6 (CH), 130.1 (CH), 136.0 (C), 145.3 (C), 163.0 (C═O), 163.1 (C═O).

Diethyl 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate (4b). White powder, mp 148–150°C, 0.31 g, yield 72%. IR (KBr) (ν_{max}/cm^{-1}): 1730 (C═O), 1695 (C═O), 1583, 1557, 1273, 1222, 764. MS (EI, 70 eV): *m/z* (%) = 258 (16), 105 (80), 77 (100). *Anal*. Calcd for $C_{25}H_{22}N_2O_5$ (430.46): C, 69.76 H, 5.15 N, 6.51%. Found: C, 69.74 H, 5.10 N, 6.60%. ^{1}H NMR: δ 1.03 (t, ^3J = 7.1, 3 H, CH_3), 1.46 (t, ^3J = 7.1, 3 H, CH_3), 4.05 (q, ^3J = 7.1, 2 H, CH_2), 4.45–4.56 (m, 2 H, CH_2), 5.88 (d, ^3J = 7.8, 1H, CH), 6.43 (d, ^3J = 7.8, 1H, CH), 6.58 (s, 1H, CH), 7.13 (d, ^3J = 7.5, 1H, CH), 7.29 (t, ^3J = 7.5, 1H, CH), 7.34 (t, ^3J = 7.4, 1H, CH), 7.38–7.40 (m, 3 H, 3 CH), 7.48 (d, ^3J = 7.6, 1H, CH), 7.68 (d, ^3J = 7.6, 2 H, 2 CH). ^{13}C NMR: δ 13.6 (CH_3), 13.9 (CH_3), 61.0 (OCH_2), 63.2 (OCH_2), 76.6 (C), 82.1 (CH), 105.8 (CH), 105.9 (C), 118.2 (CN), 122.8 (CH), 125.1 (C), 125.5 (CH), 126.7 (2 CH), 127.7 (CH), 128.1 (CH), 128.6 (2 CH), 129.5 (C), 129.6 (CH), 130.1 (CH), 136.3 (C), 145.4 (C), 162.4 (C═O) 162.5 (C═O).

Di(*tert*-butyl) 2-cyano-2-phenyl-2,11*b*-dihydro-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate (4c). Yellow powder, mp 69–71°C, 0.26 g, yield 55%. IR (KBr) (ν_{max}/cm^{-1}): 1726 and 1696 (2 C═O), 1280, 1230, 1138, 763. *Anal*. Calcd for $C_{29}H_{30}N_2O_5$ (486.56): C, 71.59 H, 6.21 N, 5.76%. Found: C, 71.68 H, 6.24 N, 5.80%. ^{1}H NMR: δ 1.29 (s, 9H, C*Me*$_3$), 1.67 (s, 9H, C*Me*$_3$), 5.78 (d, ^3J = 7.4, 1H, CH), 5.80 (s, 1H, CH), 6.43 (d, ^3J = 7.0, 1H, CH), 6.82 (d, ^3J = 6.7, 1H, CH), 7.05 (d, ^3J = 6.7, 1H, CH), 7.12 (t, ^3J = 6.7, 1H, CH), 7.25–7.26 (m, 1H, CH), 7.35–7.36 (m, 1H, CH), 7.48–7.50 (m, 3 H, 3 CH), 7.71–7.72 (m, 1H, CH). ^{13}C NMR: δ 27.7 (C*Me*$_3$), 27.8 (C*Me*$_3$), 75.1 (C), 78.0 (CH), 82.5 (*C*Me$_3$), 84.9 (*C*Me$_3$), 103.3 (C), 105.0 (CH), 119.0 (CN), 122.8 (CH), 125.1 (C), 125.2 (CH), 126.6 (C), 127.1 (CH), 127.4 (CH), 128.2 (2 CH), 128.7 (2 CH), 129.6 (CH), 129.7 (CH), 139.4 (C), 146.2 (C), 161.5 (C═O), 162.2 (C═O).

3,4-Dibenzoyl-2-phenyl-2*H*,11b*H*-[1,3]oxazino[2,3-a]isoquinoline-2-yl-cyanide (4d). Yellow powder, yield: 0.81 g (82%), mp 100–102°C. IR (KBr): ν = 1700, 1695, 1656, and 1584 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.74 (1 H, s, CH), 7.31 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.33 (4 H, m, 4 CH of C_6H_5), 7.35–7.36 (1H, m, CH), 7.48–7.50 (3 H, m, 3 CH), 7.52 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH of C_6H_5), 7.58 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.60 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.64 (4 H, m, 4 CH of C_6H_5), 7.67 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH of C_6H_5), 7.71–7.72 (m, 1H, CH), 8.02 (1 H, t, $^3J_{HH}$ = 7.9 Hz, CH), 8.06 (1 H, d, $^3J_{HH}$ = 7.9 Hz, CH), 9.58 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 75.6 (C), 82.5 (CH), 117.8 (2 CH), 118.3 (CN), 120.2 (C), 120.7 (C), 124.5 (C), 125.5 (2 CH), 126.3 (2 CH), 128.1 (2 CH), 129.1 (2 CH), 129.2 (2 CH), 129.4 (2 CH), 130.4 (2 CH), 130.5 (C), 130.7 (2 CH), 131.4 (CH), 134.2 (CH), 134.3 (C), 134.5 (CH), 138.9 (C), 139.3 (C), 192.2 (C═O), 193.8 (C═O) ppm. *Anal*. Calcd for $C_{33}H_{22}N_2O_3$ (499.55): C, 80.15; H, 4.48; N, 5.66. Found: C, 80.02; H, 4.39; N, 5.58%.

Dimethyl 3-cyano-3-phenyl-3*H*,4a*H*-[1,3]oxazino[3,2-*a*]quinoline-1,2-dicarboxylate (7a). Yellow powder, mp 138–140°C, yield: 0.60 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1775, 1752, 1748, 1538, 1345, and 1300 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 3.80 (3 H, s, MeO), 3.92 (3 H, s, MeO), 5.82 (1 H, d, $^3J_{HH}$ = 6.8 Hz, CH), 7.50 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.56 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.60 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.79 (2 H, d, $^3J_{HH}$ = 7.7 Hz, 2 CH), 8.15 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 8.21 (1 H, d, $^3J_{HH}$ = 7.7 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 51.9 (OCH_3), 52.8 (OCH_3), 75.7 (C), 83.4 (CH), 117.0 (C), 117.6 (2 CH), 118.5 (CN), 119.7 (2 CH), 124.2 (C), 125.4 (2 CH), 126.3 (C), 128.8 (2 CH), 129.2 (2 CH), 129.8 (CH), 132.4 (C), 132.8 (C), 165.1 (C═O), 175.2 (C═O) ppm. *Anal*. Calcd for $C_{23}H_{18}N_2O_5$ (402.40): C, 68.65 H, 4.51 N, 6.96%. Found: C, 68.58, H, 4.42, N, 6.85%.

Diethyl 3-cyano-3-phenyl-3*H*,4a*H*-[1,3]oxazino[3,2-*a*]quinoline-1,2-dicarboxylate (7b). Yellow powder, mp 150–152°C, yield: 0.62 g (72%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1725, 1715, 1658, 1458, 1325, and 1245 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.25 (3 H, t, ^3J = 7.3 Hz, Me), 1.32 (3 H, t, ^3J = 7.3 Hz, Me), 4.20 (2 H, q, ^3J = 7.3 Hz, CH_2O), 4.40 (2 H, q, ^3J = 7.3 Hz, OCH_2), 5.83 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.52 (2 H, d, $^3J_{HH}$ = 7.4 Hz, 2 CH), 7.62 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.64 (2 H, t, $^3J_{HH}$ = 7.3 Hz, 2 CH), 7.75 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 8.22 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 8.25 (1 H, d, $^3J_{HH}$ = 7.7 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.1 (CH_3), 14.2 (CH_3), 62.5 (OCH_2), 62.7 (OCH_2), 76.2 (C), 83.5 (CH), 117.2 (C), 118.0 (2 CH), 118.6 (CN), 120.1 (2 CH), 124.5 (C), 125.6 (2 CH), 126.7 (C), 129.2 (2 CH), 129.5 (2 CH), 130.4 (CH), 132.5 (C), 133.4 (C), 164.8 (C═O), 172.7 (C═O) ppm. *Anal*. Calcd for $C_{25}H_{22}N_2O_5$ (430.46): C, 69.76 H, 5.15 N, 6.51%. Found: C, 69.68, H, 5.07, N, 6.47%.

Dimethyl 2-cyano-2-phenyl-2*H*,9a*H*-pyrido[2,1-*b*][1,3]oxazin-3,4-dicarboxylate (8). Pale yellow powder, mp 127–129°C, yield: 0.54 g (76%). IR (KBr) (ν_{max}/cm^{-1}): 1785, 1770, 1725, 1652, 1447, and 1254 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 3.63 (s, 3 H, MeO), 3.85 (s, 3 H, MeO), 5.83 (1 H, d, $^3J_{HH}$ = 7.1 Hz, CH), 7.14 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.47 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.52 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.62 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.64 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH), 8.47 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 9.51 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.2 (OCH_3), 52.7 (OCH_3), 78.6 (CH), 80.2 (C), 104.3 (CH), 113.8 (C), 111.4 (CH), 116.9 (CH), 119.0 (CN), 120.1 (C), 120.4 (CH), 124.7 (CH), 124.8 (CH), 128.3 (CH), 129.4 (C), 130.2 (CH), 134.3 (CH), 163.3 (C═O), 164.6 (C═O) ppm. *Anal*. Calcd for $C_{19}H_{16}N_2O_5$ (352.34): C, 64.77; H, 4.58; N, 7.95. Found: C, 64.68; H, 4.47; N, 7.86%.

Dimethyl 7-cyano-1-methyl-7-phenyl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (9). Yellow powder, mp 145–147°C, yield: 0.58 g (82%). IR (KBr) (ν_{max}/cm^{-1}): 1765, 1758, 1735, 1654, 1429, and 1254 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, NMe), 3.58 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 6.54 (1 H, s, CH), 6.76 (d, 1 H, ^3J = 8.5 Hz, CH), 6.86 (d, 1 H, ^3J = 9.8 Hz, CH), 7.03 (t, 1 H, ^3J = 7.4 Hz, CH), 7.12 (d, 1 H, ^3J = 5.4 Hz, CH), 7.24 (m, 2 H, 2 CH), 7.42 (d, 1 H, ^3J = 5.4 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 36.5 (NMe), 51.5 (MeO), 52.8 (MeO), 75.4 (C), 100.3 (2 CH), 105.8 (2 CH), 112.4 (2 C), 118.5 (CN), 121.8 (CH), 129.0 (CH), 132.4 (2 CH), 140.1 (C), 163.4 (C═O), 165.8 (C═O) ppm. *Anal*. Calcd for $C_{18}H_{17}N_3O_5$ (355.35): C, 60.84; H, 4.82; N, 11.83. Found: C, 60.89; H, 4.87; N, 11.90%.

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