Domino [3+2] Cycloaddition/Annulation Reactions of β-(2-Aminophenyl)-α,β-ynones with Nitrile Oxides: Synthesis of Isoxazolo[4,5-*c*]quinolines

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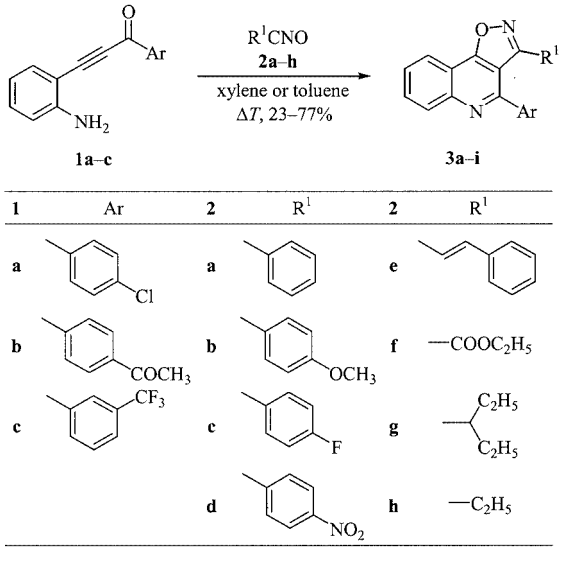
β-(2-Aminophenyl)-α,β-ynones react with nitrile oxides by domino [3+2] cycloaddition/annulation reactions giving rise to isoxazolo[4,5-*c*]quinolines in satisfactory yields.

The readily available β-(2-aminophenyl/pyridinyl)-α,β-ynones are emerging as versatile building blocks for the construction of nitrogen-containing heterocyclic rings.[1] In particular, their domino cycloaddition/annulation reactions could provide an interesting synthetic tool for building up fused mixed heteroaromatic compounds. Indeed, the domino [2+2] cycloaddition/annulation reactions of β-(2-aminophenyl)-α,β-ynones **1** with enamines accomplished the synthesis of quinolines, *c*-fused with different-size carbocyclic rings.[2a] Moreover, we reported, as a preliminary result, that sequential 1,3-dipolar cycloaddition/annulation reactions of **1** with *p*-nitrophenyl azide and benzonitrile oxide can lead to triazolo[4,5-*c*]quinoline and isoxazolo[4,5-*c*]quinoline derivatives, respectively. The development of new synthetic methods for the construction of polycyclic quinoline ring systems is still an attractive research area because these nuclei occur in pharmacologically active substances.[3] Then, a further investigation on the reactivity of β-(2-aminophenyl)-α,β-ynones **1** towards nitrile oxides, derived from different substituted aldehydes, promises to provide a clean, mild, and general synthesis of functionalised isoxazolo[4,5-*c*]quinolines and to overcome some of the drawbacks caused by the drastic reaction conditions required by traditional synthetic methods.[4] It should be pointed out that to date, only two reports dealing with the synthesis of these derivatives have appeared in the literature, both requiring harsh reaction conditions. For example, Staskun[4a] prepared 3-methyl-4-phenylisoxazolo[4,5-*c*]quinoline by heating 2-phenyl-3-acetyl-4(1*H*)-quinolone oxime above its melting point (290 °C). Recently, a number of isoxazoloquinolines have been identified as MRP1 inhibitors[5] and a new class of isoxazoloacridines and isoxazoloquinolines was prepared as potential acetylcholinesterase inhibitors.[6] Despite their importance, the limited synthetic methodologies for their construction may represent the bottleneck for further studies and developments in medicinal chemistry. Thus, in analogy to our previous work, we are pleased to report that functionalized isoxazolo[4,5-*c*]quinolines **3a**−**g** can be easily synthesised by slow dropwise addition of a solution of the appropriate α-chlorooxime (1.2 mmol) in dry xylene to a boiling solution of β-(2-aminophenyl)-α,β-ynones **1a**−**c** (1.0 mmol) and triethylamine (TEA) (1.5 mmol) in dry xylene (Scheme 1, Table 1, method A). After usual work up, the reaction mixture was purified by flash chromatography on silica gel to yield the isoxazolo[4,5-*c*]quinolines in satisfactory yields.



Scheme 1

The suggested reaction mechanism involves a regioselective [3+2] cycloaddition reaction of the ynone with the ni-

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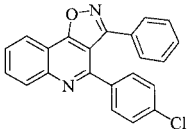
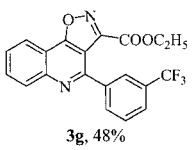
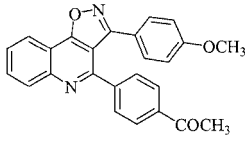
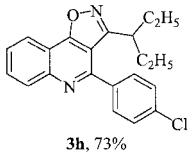
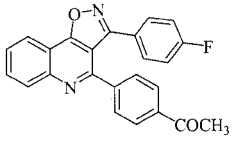
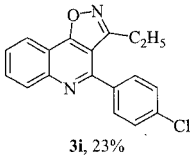
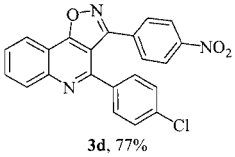
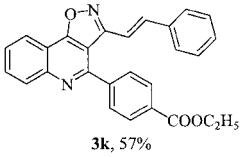
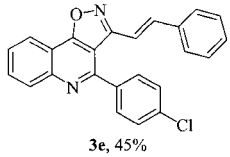
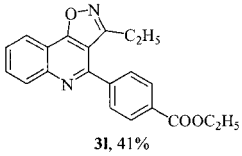
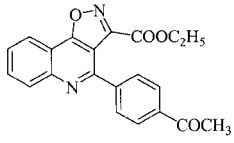
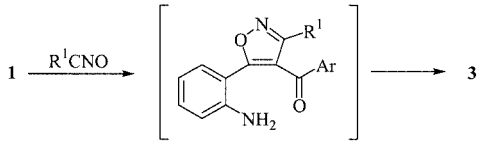
Table 1. Isoxazolo[4,5-*c*]quinolines **3a**−**l**

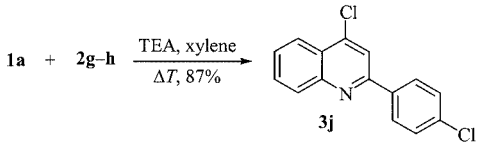
Method	Product	Method	Product
A	 **3a**, 71%	A	 **3g**, 48%
A	 **3b**, 63%	B	 **3h**, 73%
A	 **3c**, 69%	B	 **3i**, 23%
A	 **3d**, 77%	C	 **3k**, 57%
A	 **3e**, 45%	C	 **3l**, 41%
A	 **3f**, 55%		

trile oxide, generated in situ from the corresponding α-chlorooxime, followed by an intramolecular addition/elimination reaction between the amino and carbonyl groups, with loss of water. The observed regioselectivity is in agreement with the results obtained in the cycloadditions of disubstituted electron-deficient alkynes with nitrile oxides giving rise to isoxazoles carrying the electron-withdrawing group in the 4-position (Scheme 2).[7]



Scheme 2

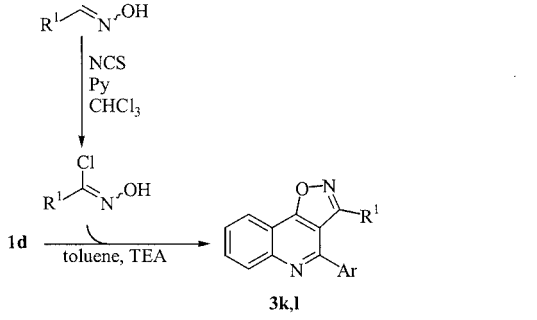
Under these standard conditions the alkanenitrile oxides **2g**−**h**, generated in situ from the corresponding α-chloro oxime, undergo dimerization to the corresponding furoxans[8] and the competitive nucleophilic addition/annulation[2b] of **1a** promoted by the chloride ion gave **3j** (Scheme 3).



Scheme 3

With the aim to avoid or minimise the dimerization to furoxanes of labile nitrile oxides, we carried out the reactions involving alkanenitrile oxides **2g**−**h** in toluene at 40 °C (Scheme 1, Table 1, method B). Under these milder conditions the isoxazolo[4,5-*c*]quinoline **3h** was isolated in 73% yield, whereas the isoxazolo[4,5-*c*]quinoline **3i** was isolated as the main reaction product in 23% yield, beside several unidentified products.

Finally, to keep the method as simple as possible and to test the possibility to further improve the reaction yields, we briefly investigated the development of a one-pot procedure starting from **1** and generating the α-chloro oxime from the corresponding oxime and, subsequently the nitrile oxide, in the same reaction step. Thus, a solution of the crude α-chloro oxime, obtained by treating the appropriate oxime with *N*-chlorosuccinimide (NCS) at 0 °C in chloroform and in the presence of a catalytic amount of pyridine (Py), was added dropwise at 40 °C, over a period of 30 min, to a solution of **1d** and triethylamine in toluene. Under these conditions **1d** reacts with **2e** and **2h** giving rise to the isoxazolo[4,5-*c*]quinolines **3k** and **3l** in 57 and 41% yields, respectively (Scheme 4, Table 1, method C).



Scheme 4

In summary, we have shown that the sequential [3+2] cycloaddition of readily available β-(2-aminophenyl)-α,β-ynones with nitrile oxides, followed by an annulation reaction, leads in satisfactory yields to isoxazolo[4,5-*c*]quinolines.

Experimental Section

General Remarks: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Merck silica gel 60 F_{254} thin-layer plates were employed for thin layer chromatography (TLC). Merck silica gel (230−400 mesh) was employed for flash column chromatography. Melting points, measured with a Stuart Scientific SMP3 apparatus, are uncorrected. Infrared spectra were recorded with an FT-IR Perkin−Elmer SPECTRUM ONE spectrophotometer, using thin films between NaCl plates in the cases of liquid samples and KBr tablets for solid samples. ^{1}H NMR spectra were recorded at room temp. in $CDCl_3$, with a Varian-Gemini 200 at 200 MHz, using residual chloroform as the internal reference (δ_H = 7.27 ppm). ^{13}C NMR spectra were recorded at room temp. in $CDCl_3$, with the same spectrometer, at 50.3 MHz, using the central peak of chloroform as the internal reference (δ_C = 77.3 ppm). Low-resolution mass spectra were run with a Fisons MD 800 spectrometer using the EI method. α,β-Ynones **1a−d** were prepared according to a described method.[9] Oximes and α-chloro oximes were synthesised according to literature procedures or purchased from standard chemical suppliers. "PE" refers to the fraction of petroleum ether with boiling range of 40−60 °C. "EtOAc" means ethyl acetate.

Reactions of α,β-Ynones 1a−c with Nitrile Oxides 2a−h (Method A): A solution of the appropriate α-chloro oxime (1.2 mmol) in dry xylene (5 mL) was slowly added to a boiling, nitrogen-flushed and well-stirred solution of the α,β-ynone **1a−c** (1.0 mmol) and TEA (1.5 mmol) in dry xylene (5 mL). The reaction mixture was stirred under reflux for 3−24 h, until no more α,β-ynone was detectable by TLC. The solvent was then removed in vacuo, the residue taken up in EtOAc and washed twice with a solution of 0.1 N HCl. Finally, the organic layer was dried with anhydrous sodium sulfate and freed from solvent under reduced pressure at 40 °C. The crude product was purified by flash chromatography on a silica gel column.

4-(4-Chlorophenyl)-3-phenylisoxazolo[4,5-*c*]quinoline (3a): Reaction time: 6 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 253 mg, 71%. Yellowish solid. M.p. 186−188 °C. IR (KBr): $\tilde{\nu}$ = 1650, 1630, 1590, 1090 cm^{-1}. ^{1}H NMR: δ = 7.15 (d, *J* = 8.5 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.26 (m, 4 H, arom.), 7.34 (d, *J* = 8.5 Hz, 2 H, 2 H, arom., BB′ part of an AA′BB′ system), 7.42 (m, 1 H, arom.), 7.76 (m, 1 H, arom.), 7.91 (m, 1 H, arom.), 8.31 (d, *J* = 8.3 Hz, 1 H, arom.), 8.48 (dd, *J* = 8.1, 1.1 Hz, 1 H, arom) ppm. ^{13}C NMR: δ = 112.2, 114.7, 121.9, 128.1, 128.3, 128.5, 128.7, 129.9, 130.2, 130.3, 131.3, 132.0, 135.9, 136.5, 147.7, 154.9, 159.2, 167.9 ppm. EI-MS: *m*/*z* (%) = 358 (37) [M$^+$ + 2], 356 (100) [M$^+$]. $C_{22}H_{13}ClN_2O$ (356.80): calcd. C 74.16, H 3.68, N 7.87; found C 74.20, H 3.65, N 7.82.

4-(4-Acetylphenyl)-3-(4-methoxyphenyl)isoxazolo[4,5-*c*]quinoline (3b): Reaction time: 24 h. Eluent for chromatography: PE/TEA (8:2). Yield: 248 mg, 63%. Yellow solid. M.p. 151−152 °C. IR (KBr): $\tilde{\nu}$ = 1673, 1609, 1514, 1356, 1268, 1251 cm^{-1}. ^{1}H NMR: δ = 2.62 (s, 3 H, CH_3C=O), 3.89 (s, 3 H, CH_3O), 6.73 (d, *J* = 8.8 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.19 (d, *J* = 8.8 Hz, 2 H, arom., BB′ part of an AA′BB′ system), 7.56 (d, *J* = 8.2 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.82 (d, *J* = 8.2 Hz, 2 H, arom., BB′ part of an AA′BB′ system), 7.84 (m, 1 H, arom.), 7.95 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1 H, arom.), 8.35 (d, *J* = 8.0 Hz, 1 H, arom.), 8.52 (d, *J* = 7.8 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 26.8, 55.5, 111.9, 113.8, 114.5, 120.0, 121.6, 127.9, 129.9, 130.0, 130.9, 131.6, 137.2, 142.1, 147.3, 154.6, 158.4, 161.0, 167.5, 197.7 (one signal obscured) ppm. $C_{25}H_{18}N_2O_3$ (394.42): calcd. C 76.13, H 4.60, N 7.10; found C 76.02, H 4.57, N 7.13.

4-(4-Acetylphenyl)-3-(4-fluorophenyl)isoxazolo[4,5-*c*]quinoline (3c): Reaction time: 5 h. Eluent for chromatography: PE/TEA (8:2). Yield: 263 mg, 69%. Light yellow solid. M.p. 214−215 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1680, 1603, 1516, 1438, 1267, 1226 cm^{-1}. ^{1}H NMR: δ = 2.63 (s, 3 H, CH_3C=O), 6.93 (t, *J* = 8.4 Hz, 2 H, arom.), 7.27 (m, 2 H, arom.), 7.54 (d, *J* = 8.1 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.82 (d, *J* = 8.1 Hz, 2 H, arom., BB′ part of an AA′BB′ system), 7.84 (m, 1 H, arom.), 7.98 (t, *J* = 7.3 Hz, 1 H, arom.), 8.29 (d, *J* = 8.1 Hz, 1 H, arom.), 8.53 (d, *J* = 7.4 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 26.8, 111.8, 114.4, 115.1 (d, $^2J_{C,F}$ = 21 Hz), 121.6, 124.0 (d, $^4J_{C,F}$ = 4 Hz), 128.0, 128.1, 130.0, 131.5 (d, $^3J_{C,F}$ = 8 Hz), 131.8, 137.4, 142.0, 147.4, 154.3, 157.9, 131.5 (d, $^1J_{C,F}$ = 248 Hz), 167.6, 197.5 ppm (one signal obscured). $C_{24}H_{15}FN_2O_3$ (382.39): calcd. C 75.38, H 3.95, N 7.33; found C 75.49, H 4.00, N 7.31.

4-(4-Chlorophenyl)-3-(4-nitrophenyl)isoxazolo[4,5-*c*]quinoline (3d): Reaction time: 8 h. Eluent for chromatography: PE/EtOAc (9:1). Yield: 309 mg, 77%. Yellowish solid. M.p. 184−185 °C. IR (KBr): $\tilde{\nu}$ = 1633, 1605, 1590, 1540, 1380 cm^{-1}. ^{1}H NMR: δ = 7.23 (d, *J* = 8.3 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.39 (d, *J* = 8.3 Hz, 2 H, 2 H, arom., BB′ part of an AA′BB′ system), 7.51 (d, *J* = 8.4 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.82 (m, 1 H, arom.), 7.98 (dt, *J* = 7.7, 1.1 Hz, 1 H, arom.), 8.17 (d, *J* = 8.4 Hz, 2 H, 2 H, arom., BB′ part of an AA′BB′ system), 8.36 (d, *J* = 8.0 Hz, 1 H, arom.), 8.54 (d, *J* = 8.5 Hz, 1 H, arom) ppm. ^{13}C NMR: δ = 111.3, 114.1, 121.6, 123.4, 128.2, 128.5, 130.0, 130.6, 130.8, 132.1, 134.5, 136.1, 136.2, 147.5, 148.7, 153.8, 157.1, 168.0 ppm. $C_{22}H_{12}ClN_3O_3$ (401.80): calcd. C 65.76, H 3.01, N 10.46; found C 65.65, H 3.05, N 10.39.

4-(4-Chlorophenyl)-3-styrylisoxazolo[4,5-*c*]quinoline (3e): Reaction time: 5 h. Eluent for chromatography: PE/EtOAc (95:5). Yield: 172 mg, 45%. Yellow solid. M.p. 168−173 °C. IR (KBr): $\tilde{\nu}$ = 1632, 1590 cm^{-1}. ^{1}H NMR: δ = 6.76 (d, *J* = 16.1 Hz, 1 H, =CH), 7.30−7.46 (m, 5 H, arom.), 7.50 (d, *J* = 16.1 Hz, 1 H, =CH), 7.60 (d, *J* = 8.4 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.76 (m, 1 H, arom.), 7.78 (d, *J* = 8.4 Hz, 2 H, 2 H, arom., BB′ part of an AA′BB′ system), 7.93. (dt, *J* = 6.9, 1.4 Hz, 1 H, arom.), 8.33 (d, *J* = 8.0 Hz, 1 H, 1 H, arom.), 8.48 (d, *J* = 6.9 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 112.2, 113.7, 114.4, 121.6, 127.3, 127.8, 128.9, 129.0, 129.5, 129.8, 131.1, 131.6, 135.5, 136.2, 136.9, 137.6, 147.3, 154.4, 155.4, 167.2 ppm. $C_{24}H_{15}ClN_2O$ (382.84): calcd. C 75.29, H 3.95, N 7.32; found C 75.41, H 3.91, N 7.36.

Ethyl 4-(4-Acetylphenyl)isoxazolo[4,5-*c*]quinoline-3-carboxylate (3f): Reaction time: 3 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 198 mg, 55%. Yellow solid. M.p. 107−108 °C. IR (KBr): $\tilde{\nu}$ = 1736, 1684, 1677, 1633, 1383, 1282, 1289, 1211 cm^{-1}. ^{1}H NMR: δ = 1.05 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.69 (s, 3 H, CH_3), 4.08 (q, *J* = 7.0 Hz, 2 H, CH_2), 7.82 (m, 1 H, arom.), 7.86 (d, *J* = 8.1 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.98 (t, *J* = 6.9 Hz, 1 H, arom.), 8.15 (d, *J* = 8.1 Hz, 2 H, arom., BB′ part of an AA′BB′ system), 8.37 (d, *J* = 7.8 Hz, 1 H, arom.), 8.50 (d, *J* = 8.0 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 13.7, 27.2, 63.3, 110.7, 113.8, 121.6, 128.6, 128.7, 129.4, 130.3, 132.5, 138.0, 143.2, 147.5, 152.0, 153.6, 160.1, 167.5, 197.7 ppm. $C_{21}H_{16}N_2O_4$ (360.36): calcd. C 69.99, H 4.48, N 7.77; found C 69.84, H 4.46, N 7.80.

Ethyl 4-[3-(Trifluoromethyl)phenyl]isoxazolo[4,5-*c*]quinoline-3-carboxylate (3g): Reaction time: 3 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 185 mg, 48%. Yellow wax. IR (NaCl): $\tilde{\nu}$ = 1739, 1633 cm^{-1}. ^{1}H NMR: δ = 1.14 (t, *J* = 7.3 Hz, 3 H, CH_3),

4.19 (q, J = 7.3 Hz, 2 H, CH_2), 7.71 (t, J = 7.3 Hz, 1 H, arom.), 7.82 (m, 2 H, arom.), 8.00 (m, 3 H, arom.), 8.37 (d, J = 8.7 Hz, 1 H, arom.), 8.51 (d, J = 8.1 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 13.6, 63.2, 110.6, 113.8, 121.6, 123.9 (q, $^1J_{C,F}$ = 272 Hz), 125.8 (q, $^3J_{C,F}$ = 4 Hz), 126.5 (q, $^3J_{C,F}$ = 4 Hz), 128.4, 129.2, 130.1, 131.1 (q, $^2J_{C,F}$ = 32 Hz), 132.1, 132.3, 139.6, 147.5, 151.7, 153.2, 159.8, 167.6 ppm. $C_{20}H_{13}F_3N_2O_3$ (386.32): calcd. C 62.18, H 3.39, N 7.25; found C 62.05, H 3.36, N 7.28.

4-Chloro-2-(4-chlorophenyl)quinoline (3j): Reaction time: 18 h. Eluent for chromatography: PE/EtOAc (95:5). Yield: 238 mg, 87%. Yellowish solid. M.p. 125−126 °C. IR (KBr): $\tilde{\nu}$ = 1588, 1571, 1544, 1486, 1091 cm^{-1}. ^{1}H NMR: δ = 7.53 (d, J = 8.6 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.66 (ddd, J = 8.4, 6.9, 1.2 Hz, 1 H, arom.), 7.82 (ddd, J = 8.4, 6.9, 1.4 Hz, 1 H, arom.), 7.96 [s, 1 H, 3-H, arom.), 8.13 (d, J = 8.6 Hz, 2 H, 2 H, arom., BB′ part of an AA′BB′ system), 8.19 (m, 1 H, arom.), 8.25 (dd, J = 8.4, 1.2 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 118.7, 124.1, 125.4, 127.5, 128.8, 129.2, 130.1, 130.8, 136.2, 137.1, 143.4, 149.1, 156.0 ppm. EI-MS: m/z (%) = 275 (58) [M$^+$ + 2], 273 (92) [M$^+$], 238 (100) [M$^+$ − Cl], 203 [M$^+$ − 2 Cl] (58). $C_{15}H_9Cl_2N$ (274.14): calcd. C 65.72, H 3.31, N 5.11; found C 65.64, H 3.29, N 4.99.

Reactions of α,β-Ynone 1a with Nitrile Oxides 2g−h (Method B): A solution of the appropriate α-chloro oxime (1.2 mmol) in dry toluene (5 mL) was slowly added to a nitrogen-flushed and well-stirred solution of the α,β-ynone **1a−c** (1.0 mmol) and TEA (1.5 mmol) in dry toluene (5 mL). The reaction mixture was stirred at 40 °C for 24 h. The solvent was then removed in vacuo, the residue taken up in EtOAc and washed twice with a solution of 0.1 N HCl. Finally, the organic layer was dried with anhydrous sodium sulfate and freed from solvent under reduced pressure at 40 °C. The crude product was purified by flash chromatography on a silica gel column [PE/EtOAc (98:2)].

4-(4-Chlorophenyl)-3-(1-ethylpropyl)isoxazolo[4,5-*c*]quinoline (3h): Yield: 256 mg, 73%. Yellowish oil. IR (NaCl): $\tilde{\nu}$ = 1634, 1600, 1558, 1520, 1090 cm^{-1}. ^{1}H NMR: δ = 0.77 (t, J = 7.3 Hz, 6 H, CH_3), 1.70 (m, 4 H, CH_2), 2.78 (m, 1 H, CH), 7.58 (m, 4 H, arom.), 7.75 (m, 1 H, arom.), 7.89 (m, 1 H, arom.), 8.28 (d, J = 8.4 Hz, 1 H, arom.), 8.46 (d, J = 8.1 Hz, 1 H, arom) ppm. ^{13}C NMR: δ = 11.7, 26.9, 40.2, 113.6, 114.6, 121.6, 127.6, 128.8, 129.7, 130.4, 131.3, 135.7, 137.5, 147.0, 154.9, 131.8, 166.6 ppm. $C_{21}H_{19}ClN_2O$ (350.84): calcd. C 71.89, H 5.46, N 7.98; found C 71.67, H 5.49, N 8.02.

4-(4-Chlorophenyl)-3-ethylisoxazolo[4,5-*c*]quinoline (3i): Yield: 71 mg, 23%. Yellow solid. M.p. 124−125 °C. IR (KBr): $\tilde{\nu}$ = 1634, 1596, 1556, 1088 cm^{-1}. ^{1}H NMR: δ = 1.15 (t, J = 7.5 Hz, 3 H, CH_3), 1.70 (q, J = 7.5 Hz, 2 H, CH_2), 7.57 (d, J = 8.8 Hz, 2 H, arom., AA′ part of an AA′BB′ system), 7.66 (d, J = 8.8 Hz, 2 H, arom., BB′ part of an AA′BB′ system), 7.74 (m, 1 H, arom.), 7.89 (m, 1 H, arom.), 8.29 (d, J = 8.4 Hz,, 1 H, arom.), 8.43 (d, J = 8.1 Hz, 1 H, arom) ppm. ^{13}C NMR: δ = 12.0, 20.8, 113.0, 114.6, 121.7, 127.8, 129.0, 129.9, 130.5, 131.6, 136.1, 137.6, 147.4, 154.9, 159.9, 167.1 ppm. $C_{18}H_{13}ClN_2O$ (308.76): calcd. C 70.02, H 4.24, N 9.07; found C 70.05, H 4.24, N 9.06.

One-Pot Reactions of α,β-Ynone 1d with Nitrile Oxides 2e,h (Method C): To a well-stirred solution of 3-phenylpropenal oxime or propionaldehyde oxime (1.63 mmol) in chloroform (4 mL) and pyridine (0.02 mL), cooled to 0 °C, *N*-chlorosuccinimide (217 mg, 1.63 mmol) was added portionwise over a period of 30 min. The mixture was treated at room temperature for 2 h, until the starch-iodide paper test was negative, then diluted with toluene (10 mL) and added dropwise at 40 °C, over a period of 4 h, to a solution containing the α,β-ynone **1d** (239 mg, 0.81 mmol) and triethylamine (197 mg, 1.95 mmol) in toluene (6 mL). The mixture was then stirred at 40 °C overnight, concentrated to dryness, taken up in EtOAc (60 mL) and washed twice with a solution of 0.1 N HCl (2 × 40 ml). The organic layer was finally dried with anhydrous sodium sulfate, freed from the solvent under reduced pressure and the crude product was purified by flash chromatography on a silica gel column [PE/EtOAc (95:5)].

Ethyl 4-(3-Styrylisoxazolo[4,5-*c*]quinolin-4-yl)benzoate (3k): Yield: 194 mg, 57%. Yellow solid. M.p. 159−160 °C. IR (KBr): $\tilde{\nu}$ = 1716, 1600, 1438 cm^{-1}. ^{1}H NMR: δ = 1.48 (t, J = 7.0 Hz, 3 H, CH_3), 4.49 (q, J = 7.0 Hz, 2 H, CH_2), 6.74 (d, J = 16.5 Hz, 1 H, =CH), 7.33 (m, 5 H, arom.), 7.54 (d, J = 16.5 Hz, 1 H, =CH), 7.78 (t, J = 7.0 Hz, 1 H, arom.), 7.90 (m, 3 H, arom.), 8.30 (m, 3 H, arom.), 8.45 (d, J = 6.5 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 14.4, 61.4, 113.6, 114.4, 121.5, 127.3, 127.9, 28.9, 129.4, 129.8, 131.6, 131.7, 135.5, 137.6, 142.4, 147.1, 154.5, 155.4, 166.2, 167.2 (3 signals obscured) ppm. EI-MS: m/z (%) = 420 (100) [M$^+$]. $C_{27}H_{20}N_2O_3$ (420.47): calcd. C 77.13, H 4.79, N 6.66; found C 76.32, H 4.75, N 6.52.

Ethyl 4-(3-Ethylisoxazolo[4,5-*c*]quinolin-4-yl)benzoate (3l): Yield: 126 mg, 45%. Yellow solid. M.p. 122−124 °C. IR (KBr): $\tilde{\nu}$ = 1716, 1600, 1570 cm^{-1}. ^{1}H NMR: δ = 1.05 (t, J = 7.2 Hz, 3 H, CH_3), 1.48 (t, J = 7.0 Hz, 3 H, CH_3), 2.80 (q, J = 7.2 Hz, 2 H, CH_2), 4.47 (q, J = 7.2 Hz, 2 H, CH_2O), 7.78 (m, 3 H, arom.), 7.93 (t, J = 6.9 Hz, 1 H, arom.), 8.28 (d, J = 8.4 Hz, 2 H, arom.), 8.36 (d, J = 8.5 Hz, 1 H, arom.), 8.46 (d, J = 6.9 Hz, 1 H, arom.) ppm. ^{13}C NMR: δ = 11.8, 14.4, 20.6, 61.5, 112.9, 114.5, 121.6, 127.9, 129.0, 129.7, 128.9, 131.6, 142.8, 147.0, 154.9, 159.8, 166.2, 167.0 ppm (one signal obscured). $C_{21}H_{18}N_2O_3$ (346.38): calcd. C 72.82, H 5.24, N 8.09; found C 72.32, H 5.20, N 7.99.

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