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Synthesis of New Quinoline Derivatives

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Abstract: The synthesis of some new functionalized quinolyl derivatives has been described, based on the 1,3-dipolar cycloaddition of an azomethine ylide, generated from sarcosine or *N*-benzylglycine and paraformaldehyde, to 2-chloro-3-quinolinecarbaldehydes.

Keywords: Dipolar cycloaddition, multicomponent reactions, oxazolines, quinolines

Quinolines and their derivatives are very important in medicinal chemistry because of their wide occurrence in natural products[1] and drugs.[2] Oxazole and its derivatives also have been incorporated into a large number of compounds of potential medicinal value.[3]

The rapid and efficient generation of nitrogen-containing privileged structural motifs is a great challenge in biological, organic, and medicinal chemistry. Domino processes[4] and multicomponent reactions (MCRs)[5]

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offer excellent avenues to face these challenges. As a part of our research program aimed at synthesizing nitrogen-containing druglike heterocyles by the combined use of domino and multicomponent reactions, we became interested in the oxazolidine-coupled quinoline molecules **3**.

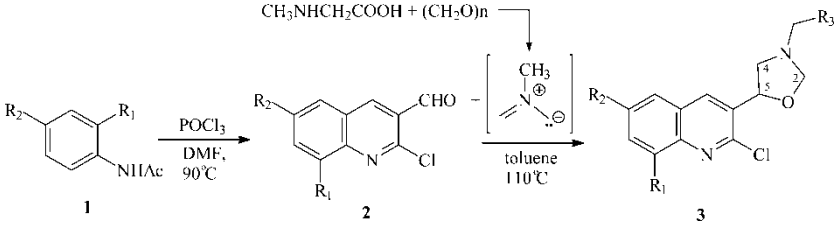
RESULTS AND DISCUSSION

The starting quinolines (**2a**–**d**) for the MCR were prepared by the method described by O. Meth-Cohn from the corresponding acetanilides by the treatment with the Vilsmeier reagent in a very effective domino reaction.[6]

Recently we have described the three-component reaction of aromatic aldehydes, sarcosine, and paraformaldehyde, with a view to preparing 3-methyl-5-aryl-oxazolidines, which were valuable intermediates for further elaboration to 2-dimethylamino-1-phenylethanols.[7] This process utilizes a 1,3-dipolar cycloaddition reaction, which generally affords a simple and convenient method for the regio- and stereoselective construction of a variety of complex pyrrolidine derivatives. However, the azomethine ylides can react with C═O double bonds in 1,3-dipolar cycloadditions, and several oxazolidine-type cycloadducts have been described, but in these cases either (a) the aldehyde component of the azomethine ylide, formed in situ, was the same as the dipolarophile,[8] or (b) a stable precursor of the azomethine ylide was prepared in advance and this was followed by the cycloaddition step.[8a,9]

Based on these results, we synthesized with our MCR a variety of 5-(3-quinolyl)-oxazilidine **3** by simple mixing of sarcosine or N-benzylglycine, paraformaldehyde, and a 2-chloro-3-formyl-quinoline (as the dipolarophile) in toluene and refluxing under Dean–Stark conditions (Scheme 1). In all cases only the formaldehyde served as a component for the nonstabilized azomethine ylide generation, and the cycloadduct **3a**–**h** was isolated in good yield as the sole product (Table 1).

The heterocyclic ring structure of products **3a**–**e** was confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectral studies. The ^{1}H NMR and H-HCOSY spectra of **3c** reveal two sharp singlets at δ 2.53 and 3.92 due to the OCH_3 of the



Scheme 1.

Table 1. 1,3-Dipolar addition reaction of 2-chloro-3-formyl-quinolines (**2a**–**e**) and azomethine ylide generated from paraformaldehyde and sarcosine

Entry	R^1	R^2	R^3	Starting material	Product	Yield (%)
1	H	H	H	**2a**	**3a**	92
2	H	H	Ph	**2a**	**3b**	84
3	H	MeO	H	**2b**	**3c**	87
4	H	MeO	Ph	**2b**	**3d**	65
5	Cl	Me	H	**2c**	**3e**	95
6	Cl	Me	Ph	**2c**	**3f**	80
7	Me	H	H	**2d**	**3g**	91
8	Me	H	Ph	**2d**	**3h**	78

quinoline and *N*-methyl oxazolidine protons. Both of the $N-CH_2$ proton of H-4 appeared as a doublet of a doublet at δ 3.62 and 2.85 ($J = 6.7$ and 11.3 Hz). The H-5 proton exhibited as triplet at δ 5.35 with $J = 6.5$ Hz. Two doublets appeared in the region δ 4.66–4.53 ($J = 5.1$ Hz) for H-2 protons.

The aromatic protons of the quinoline ring appeared as in the region of δ 8.26–7.29 with the expected pattern. The ^{13}C NMR spectra of **3c** exhibited peaks at δ 89.3, 73.6, and 61.4 ppm for the oxazolidine ring carbons. The peaks at δ 55.5 ppm and at δ 41.7 ppm are due to the oxazolidine *N*-methyl and methoxy carbons of the quinoline ring respectively.

In conclusion, we have developed a new, two-step route by the combined use of domino and multicomponent reactions from simple starting materials for the synthesis of a 3-quinolyl-1,3-oxazolone ring system via the 1,3-dipolar cycloaddition reaction of nonstabilized azomethine ylides to aldehydes. This oxazolidines could be valuable building blocks of other compunds of general interest.[10]

EXPERIMENTAL

General

Column chromatography was performed using Merck Kieselgel 60 70–230 mesh and thin-layer chromatography (TLC) on aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml of concn. sulphuric acid, and 1 ml of anisaldehyde) and heated at ca. 150°C. Phosphoryl chloride (Aldrich) and *N,N*-dimethylformamide, anhydrous (Aldrich) were used as received. All solvents were purified according to standard procedures. IR spectra were obtained on a Bruker Vector 22 FT-IR instrument. NMR spectra were

obtained on Varian Inova 500 and Bruker DRX-500. Chemical shifts are given relative to δ_{TMS}.

General Procedure for the Synthesis of 2-Chloro-3-quinolinecarbaldehydes (2a–d)

These compounds were prepared by the method of Meth-Cohn et al.[6] *N,N*-Dimethylformamide (9.1 g, 9.6 ml, 0.125 mol) was cooled to 0°C, and phosphoryl chloride (53.7 g, 32.2 ml, 0.35 mol) was added dropwise with stirring. To this solution was added the corresponding acetanilide (0.05 mol), and the temperature of the reaction mixture was raised to 80°C for 18 h. The cooled reaction mixture was poured into ice water (300 ml) and stirred for 1 h at 0–10°C. The precipitated 2-chloro-3-quinolinecarbaldehyde was failtered off, washed with water (100 ml), dried, and recrystallized from ethyl acetate to give the title product.

Data

2-Chloro-3-quinolinecarbaldehyde (2a): pale yellow powder (5.92 g, 62%), mp 146–147°C (lit.[6b] 148–149°C); ^{1}H NMR (500 MHz, $CDCl_3$): 10.51 (s, 1H, CHO), 8.81 (s, 1H, H-4), 8.09 (d, 1H, $J = 8.2$ Hz, H-5), 8.03 (d, 1H, $J = 8.2$ Hz, H-8), 7.92 (t, 1H, $J = 8.2$ Hz, H-6), 7.69 (t, 1H, $J = 8.2$ Hz, H-7); HRMS (E.I) $[M]^+$calcd. for $C_{10}H_6C1NO = 191.01379$; found 191.0147.

2-Chloro-6-methoxy-3-quinolinecarbaldehyde (2b): pale yellow powder (5.41 g, 49%), mp 143–144°C (lit.[6b] 145.5–146.5°C); ^{1}H NMR (500 MHz, $CDCl_3$): 10.50 (s, 1H, CHO), 8.57 (s, 1H, H-4), 7.91 (d, 1H, $J = 9.0$ Hz, H-8); 7.46 (dd, 1H, $J = 9.0$ Hz and 2.8 Hz, H-7), 7.17 (d, 1H, $J = 2.8$ Hz, H-5), 3.94 (s, 3H, OCH_3); HRMS (E.I) $[M]^+$calcd. for $C_{11}H_8C1NO_2 = 221.02436$; found 221.0261.

2,6-Dichloro-8-methyl-3-quinolinecarbaldehyde (2c): pale yellow powder (4.68 g, 39%), mp 146–148°C; ^{1}H NMR (500 MHz, $CDCl_3$): 10.55 (s, 1H, CHO), 8.61 (s, 1H, H-4), 7.78 (s, 1H, H-5), 7.67 (s, 1H, H-7), 2.77 (s, 3H, Me); ^{13}C NMR (125 MHz, $CDCl_3$): 189.1 (q), 149.2 (q), 147.2 (q), 139.3 (CH), 139.2 (q), 134.1 (CH), 133.5 (q), 127.2 (q), 126.8 (q), 125.8 (CH), 17.7 (CH_3); IR (KBr, cm^{-1}): 3050, 1693, 1628, 1582, 1379, 1038. HRMS (E.I) $[M]^+$calcd. for $C_{11}H_7C1_2NO = 238.99047$; found 238.9911.

2-Chloro-8-methyl-3-quinolinecarbaldehyde (2d): pale yellow powder (7.40 g, 72%), mp 138°C (lit.[6b] 137–138°C); ^{1}H NMR (500 MHz, $CDCl_3$): 10.52 (s, 1H, CHO), 8.64 (s, 1H, H-4), 7.76 (d, 1H, $J = 8.2$ Hz,

H-5), 7.68 (d, 1H, $J = 8.2$ Hz, H-7), 7.50 (t, 1H, $J = 8.2$ Hz, H-6), 2.75 (s, 3H, CH_3); HRMS (E.I) $[M]^+$calcd. for $C_{11}H_8C1NO = 205.02944$; found 205.0301.

General Procedure for the Cycloaddition Reaction of Azomethine Ylide Generated from Paraformaldehyde and Sarcosine or *N*-Benzyl Glycine with 2-Chloro-3-formyl-quinolines (2a–d)

The corresponding 2-chloro-3-formyl-quinoline (1 mmol), sarcosine or *N*-benzyl-glycine (2 mmol), and paraformaldehyde (5 mmol), were suspended in toluene (50 ml), and the reaction mixture was then heated for 10 h under Dean–Stark conditions. After the reaction was complete, it was filtered through a pad of Celite, the solvent was removed in vacuo, and the residue was purified by flash chromatography (acetone/hexane 1:3).

Data

5-(2-Chloro-3-quinolyl)-3-methyl-1,3-oxazolone (3a): pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 8.40 (s, 1H, qui-H-4), 7.97 (d, 1H, $J = 8.2$ Hz, qui-H-5), 7.68 (d, 1H, $J = 8.2$ Hz, qui-H-8), 7.55 (t, 1H, $J = 8.2$ Hz, qui-H-6), 7.50 (t, 1H, $J = 8.2$ Hz, qui-H-7), 5.35 (t, 1H, $J = 6.9$ Hz, H-5), 4.65 (d, 1H, $J = 5.0$ Hz, H-2), 4.52 (d, 1H, $J = 5.0$ Hz, H-2), 3.61 (dd, 1H, $J = 6.9$ and 11.1 Hz, H-4), 2.85 (dd, 1H, $J = 6.9$ and 11.1 Hz, H-4), 2.51 (s, 3H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 148.0 (q), 146.6 (q), 146.65 (q), 134.4 (CH), 129.9 (CH), 127.9 (CH), 127.4 (CH), 127.1 (q), 126.9 (CH), 89.2 (CH_2), 73.4 (CH), 61.2 (CH_2), 41.4 (CH_3); IR (neat, cm^{-1}): 3061, 2951, 2870, 2800, 1676, 1619, 1592, 1565, 1492, 1455, 1398, 1326, 1158, 1055, 1029; HRMS (E.I) $[M]^+$calcd. for $C_{13}H_{13}C1\,N_2O = 248.07164$; found 248.0739.

5-(2-Chloro-3-quinolyl)-3-benzyl-1,3-oxazolone (3b): pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 8.36 (s, 1H, qui-H-4), 7.99 (d, 1H, $J = 7.8$ Hz, qui-H-5), 7.81 (d, 1H, $J = 7.8$ Hz, qui-H-8), 7.67 (t, 1H, $J = 7.8$ Hz, qui-H-6), 7.52 (t, 1H, $J = 7.8$ Hz, qui-H-7), 7.34–7.24 (m, 5H, Ph), 5.35 (t, 1H, $J = 7.0$ Hz, H-5), 4.67 (d, 1H, $J = 5.5$ Hz, H-2), 4.63 (d, 1H, $J = 5.5$ Hz, H-2), 3.81 (s, 2H, NCH_2), 3.74 (dd, 1H, $J = 7.0$ and 11.7 Hz, H-4), 2.86 (dd, 1H, $J = 7.0$ and 11.7 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): 148.1 (q), 146.7 (q), 138.2 (q), 134.4 (q), 134.3 (q), 129.9 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.0 (CH), 87.2 (CH_2), 73.4 (CH), 59.2 (CH_2), 58.3 (CH_2). IR (neat, cm^{-1}): 3062, 2927, 2876, 1676, 1592, 1565, 1493, 1454, 1398, 1326, 1076, 927; HRMS (E.I) $[M]^+$calcd. for $C_{19}H_{17}C1\,N_2O = 324.10294$; found 324.1001.

5-(6-Methoxy-2-chloro-3-quinolyl)-3-methyl-1,3-oxazolone (3c): pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 8.26 (s, 1H, qui-H-4), 7.89 (d, 1H, $J = 9.2$ Hz, qui-H-8), 7.35 (dd, 1H, $J = 2.8$ and 9.2 Hz, qui-H-7), 7.09 (d, 1H, $J = 2.8$ Hz, qui-H-5), 5.35 (t, 1H, $J = 6.5$ Hz, H-5), 4.66 (d, 1H, $J = 5.1$ Hz, H-2), 4.53 (d, 1H, $J = 5.1$ Hz, H-2), 3.92 (s, 3H, OCH_3), 3.62 (dd, 1H, $J = 6.7$ and 11.3 Hz, H-4), 2.85 (dd, 1H, $J = 6.7$ and 11.3 Hz, H-4), 2.53 (s, 3H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 158.2 (CH), 145.5 (q), 142.8 (q), 134.7 (CH), 133.3 (q), 129.5 (CH), 128.4 (q), 122.7 (CH), 105.2 (CH), 89.3 (CH_2), 73.6 (CH), 61.4 (CH_2), 55.5 (CH_3), 41.7 (CH_3); IR (neat, cm^{-1}): 2955, 2870, 2801, 1671, 1623, 1592, 1498, 1455, 1329, 1228, 1165, 1123, 1056, 1032, 959; HRMS (E.I) $[M]^+$calcd. for $C_{14}H_{15}C1\ N_2O_2 = 278.08220$; found 278.0852.

5-(6-Methoxy-2-chloro-3-quinolyl)-3-benzyl-1,3-oxazolone (3d): pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 8.25 (s, 1H, qui-H-4), 7.86 (d, 1H, $J = 9.2$ Hz, qui-H-8), 7.33–7.25 (m, 6H, Ph and qui-H-7), 7.06 (d, 1H, $J = 2.8$ Hz, qui-H-5), 5.33 (t, 1H, $J = 6.8$ Hz, H-5), 4.66 (d, 1H, $J = 5.5$ Hz, H-2), 3.87 (s, 3H, OCH_3), 3.81 (s, 2H, NCH_2), 3.72 (dd, 1H, $J = 6.8$ and 11.8 Hz, H-4), 3.57 (dd, 1H, $J = 6.8$ and 11.8 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): 158.0 (q), 145.4 (q), 142.6 (q), 138.2 (q), 134.5 (q), 133.1 (CH), 129.3 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.2 (q), 127.2 (CH), 122.5 (CH), 105.0 (CH), 87.1 (CH_2), 73.3 (CH), 59.2 (CH_2), 58.2 (CH_2), 55.3 (CH_3). IR (neat, cm^{-1}): 3062, 2935, 2878, 1674, 1594, 1498, 1454, 1329, 1061, 998; HRMS (E.I) $[M]^+$calcd. for $C_{20}H_{19}C1\ N_2O_2 = 354.11350$; found 354.1147.

5-(2,8-Dichloro-6-methyl-3-quinolyl)-3-methyl-1,3-oxazolone (3e): pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 8.23 (s, 1H, qui-H-4), 7.65 (d, 1H, $J = 2.1$ Hz, qui-H-5), 7.49 (d, 1H, $J = 2.1$ Hz, qui-H-7), 5.35 (t, 1H, $J = 6.5$ Hz, H-5), 4.65 (d, 1H, $J = 5.1$ Hz, H-2), 4.53 (d, 1H, $J = 5.1$ Hz, H-2), 3.56 (dd, 1H, $J = 6.5$ and 11.5 Hz, H-4), 2.84 (dd, 1H, $J = 6.5$ and 11.5 Hz, H-4), 2.73 (s, 3H, CH_3), 2.52 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 147.4 (q), 144.6 (q), 138.6 (q), 135.5 (q), 133.8 (CH), 132.4 (q), 130.8 (CH), 128.0 (q), 124.0 (CH), 89.4 (CH_2), 73.5 (CH), 61.3 (CH_2), 41.6 (CH_3), 17.6 (CH_3); IR (KBR, cm^{-1}): 3694, 2963, 2794, 1654, 1522, 1322, 1263, 1099, 1022; HRMS (E.I) $[M]^+$calcd. for $C_{14}H_{14}C1_2N_2O = 296.04831$; found 296.0499.

5-(2,8-Dichloro-6-methyl-3-quinolyl)-3-benzyl-1,3-oxazolone (3f): pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 8.24 (s, 1H, qui-H-4), 7.65 (s, 1H, qui-H-5), 7.49 (s, 1H, qui-H-7), 7.36–7.25 (m, 5H, Ph), 5.35 (t, 1H, $J = 7.0$ Hz, H-5), 4.67 (d, 1H, $J = 5.6$ Hz, H-2), 4.63 (d, 1H, $J = 5.6$ Hz, H-2), 3.83 (s, 2H, NCH_2), 3.76 (dd, 1H, $J = 7.0$ and 11.8 Hz, H-4), 3.73 (dd, 1H, $J = 7.0$ and 11.8 Hz, H-4), 2.72 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 147.4 (q), 144.6 (q), 138.6 (q), 138.3 (q), 135.4 (q), 133.8 (CH), 132.4 (q), 130.8 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 127.9

(q), 127.4 (CH), 124.1 (CH), 87.4 (CH_2), 73.4 (CH), 59.3 (CH_2), 58.4 (CH_2), 17.6 (CH_3); IR (neat, cm^{-1}): 3063, 2925, 2876, 1701, 1592, 1479, 1454, 1327, 1053, 997; HRMS (E.I) $[M]^+$calcd. for $C_{20}H_{18}C1_2N_2O = 372.07961$; found 372.0811.

5-(8-Methyl-2-chloro-3-quinolyl)-3-methyl-1,3-oxazolone (3g): pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): 8.31 (s, 1H, qui-H-4), 7.65 (d, 1H, $J = 8.1$ Hz, qui-H-5), 7.52 (d, 1H, $J = 8.1$ Hz, qui-H-7), 7.42 (t, 1H, $J =$ 8.1 Hz, qui-H-6), 5.36 (t, 1H, $J = 6.7$ Hz, H-5), 4.65 (d, 1H, $J = 5.0$ Hz, H-2), 4.53 (d, 1H, $J = 5.1$ Hz, H-2), 3.63 (dd, 1H, $J = 6.7$ and 11.5 Hz, H-4), 2.85 (dd, 1H, $J = 6.7$ and 11.5 Hz, H-4), 2.75 (s, 3H, CH_3), 2.53 (s, 3H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 147.1 (q), 146.1 (q), 136.2 (CH), 134.6 (q), 134.1 (q), 130.0 (CH), 127.3 (CH), 126.7 (q), 125.5 (CH), 89.3 (CH_2), 73.5 (CH), 61.4 (CH_2), 41.6 (CH_3), 17.7 (CH_3); IR (neat, cm^{-1}): 3010, 2952, 2860, 2806, 1653, 1599, 1576, 1485,1463, 1395, 1377, 1363, 1323, 1206, 1170, 1122, 1088, 1060, 1044, 1009; HRMS (E.I) $[M]^+$calcd. for $C_{14}H_{15}C1\ N_2O = 262.08729$; found 262.0879.

5-(8-Methyl-2-chloro-3-quinolyl)-3-benzyl-1,3-oxazolone (3h): pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): 8.32 (s, 1H, qui-H-4), 7.66 (d, 1H, $J = 7.2$ Hz, qui-H-5), 7.51 (d, 1H, $J = 7.2$ Hz, qui-H-7), 7.42 (t, 1H, $J = 7.2$ Hz, qui-H-6), 7.34–7.22 (m, 5H, Ph), 5.36 (t, 1H, $J = 6.7$ Hz, H-5), 4.67 (d, 1H, $J = 5.5$ Hz, H-2), 4.63 (d, 1H, $J = 5.5$ Hz, H-2), 3.82 (s, 2H, NCH_2), 3.74 (dd, 1H, $J = 7.2$ and 11.8 Hz, H-4), 2.86 (dd, 1H, $J = 7.2$ and 11.8 Hz, H-4), 2.74 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 147.1 (q), 146.1 (q), 138.3 (q), 136.3 (q), 134.6 (CH), 134.1 (q), 130.1 (CH), 128.6 ($2 \times$ CH), 128.4 ($2 \times$ CH), 128.4 (q), 127.3 (CH), 126.8 (CH), 125.5 (CH), 87.3 (CH_2), 73.5 (CH), 59.4 (CH_2), 58.4 (CH_2), 19.0 (CH_3); IR (neat, cm^{-1}): 3062, 2876, 1641, 1597, 1495, 1454, 1326, 1075, 905; HRMS (E.I) $[M]^+$calcd. for $C_{20}H_{19}C1\ N_2O = 338.11859$; found 338.1197.

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