Rearrangement of 2-Bromo-*N*-quinoline-8-yl-acetamide Leading to New Heterocycle

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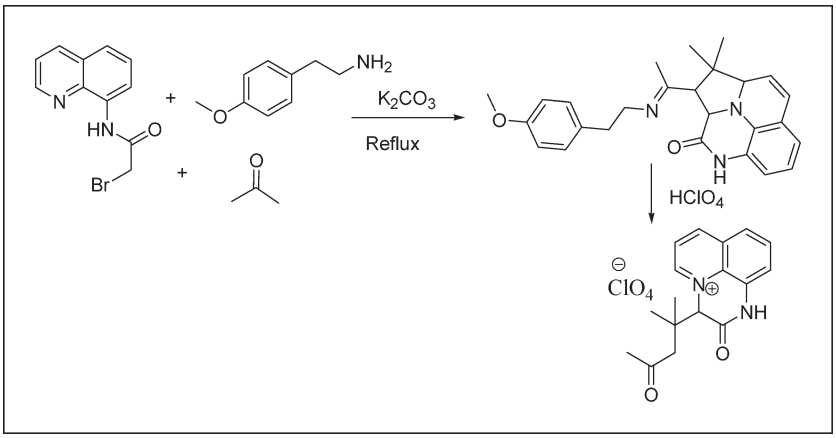

A four fused rings containing heterocyclic compound is formed in the reaction between 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(4-methoxyphenyl)ethylamine, and acetone in the presence of potassium carbonate; the heterocycle undergoes further reaction with perchloric acid to form a perchlorate salt of a quinoxaline derivative.

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INTRODUCTION

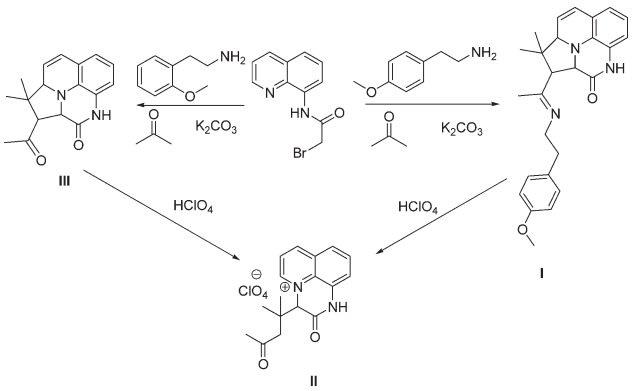
Intramolecular cyclization processes are very useful in heterocycle synthesis [1–6] and they are used for synthesis of variety of natural products and drugs. Among them, *N*-acylinium ion cyclization reactions are very attractive [7–10]. Such intramolecular reactions are carried out under catalytic conditions [11–18]. Several of these reactions require multiple steps [1]. Multicomponent reactions to prepare heterocycles help to reduce the inconvenience caused by the extra work involved in product purification [19–24] in each step and also to reduce the reaction time. We have serendipitously observed formation of a heterocycle from a reaction of 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(4-methoxyphenyl)ethylamine and acetone. The characterization of the fused four-member heterocyle along with its subsequent rearrangement to a quinoxaline derivative is described here. Some quinoxaline derivatives [1] have medicinal value, so new method of synthesis for such compounds are desirable.

RESULTS AND DISCUSSION

A multicomponent reaction between 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(4-methoxyphenyl)ethylamine, and acetone in the presence of potassium carbonate gives a fused ring heterocyclic compound **I** as illustrated in Scheme 1. However, analogous multicomponent reaction between 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(2-methoxyphenyl)ethylamine, and acetone in the presence of potassium carbonate gives a fused ring heterocyclic carbonyl compound **III**, not the imine that was obtained while 2-(4-methoxyphenyl)ethylamine was used. This compound transforms to perchlorate salt **II** of another heterocycle on reaction with perchloric acid. The compound **III** also undergoes rearrangement reaction with perchloric acid to form perchlorate salt **II**. The use of excess acetone in these reactions serves dual purposes of reactant as well as solvent.

All these compounds were characterized from their spectroscopic properties. The compound **I** has IR absorptions at 1676 cm^{-1} and at 1635 cm^{-1} due to carbonyl and C=N stretching, respectively. The high resolution mass spectrum of the compound shows the mass for the M^+ peak at 415.2688, that supports the composition. The ^1H NMR and ^{13}C NMR of the compounds have the desirable numbers of peaks to support the structure (for assignments of peaks please refer to supporting figures). The compound **I** is further characterized by X-ray crystallography and the structure of the compound is shown in Figure 1(a).

Scheme 1. Reaction leading to product **I** and **III**, which react with perchloric acid to form salt **II**.



As mentioned the compound **I** undergoes hydrolysis followed by ring opening reactions to give a quinoxaline derivative in the form of a perchlorate salt **II**. The salt **II** is characterized by conventional spectroscopic techniques as well as by X-ray crystallography [Fig. 1(b)]. The IR spectra of the salt **II** have characteristic sharp perchlorate absorption at 1100 cm^{-1} and its carbonyl absorption appears at 1705 cm^{-1}.

Plausible reaction paths (Scheme 2) for the formation of the compound **I** may be through an initial condensation reaction of two molecules of acetone to form aldol type intermediate. The carbonyl group of the aldol gets condensed with 2-(4-methoxyphenyl)ethylamine to form an imine derivative as an intermediate species. This imine containing molecule has a hydroxy group, which is attached to a tertiary carbon and it would like to form C—C bond with the quinoiline ring through elimination of a water molecule. Presumably, this intermediate compound forms a bromide salt through cyclization reaction. The cyclized product thus formed, undergo a hydride shift to form a derivative that is suitable for further nucleophilic attack of an anion generated next to the C=N group. It forms the desired product **I**. Thus, by these reaction steps, two additional rings over the quinoline rings are constructed. The added advantage of this reaction is that it does not stop at the stage of formation of one ring, but continues to form multiple rings; that generally does not happen in intramolecular cyclization reactions [2–6].

The formation of the salt **II** can be explained by a three steps mechanistic path as illustrated in Scheme 2. The first step could be the generation of ketone from a hydrolytic reaction of perchloric acid by the conversion of imine to keto group. The keto group containing compound thus formed gets protonated under acidic condition to form enolised form of a cationic species with perchlorate as a counter anion. This process leads to opening of the five-member ring of the parent compound. The enolic cation thus formed, on aromatization leads to concomitant cleavage of a C—C bond along with the formation of a new C—C bond at a tertiary

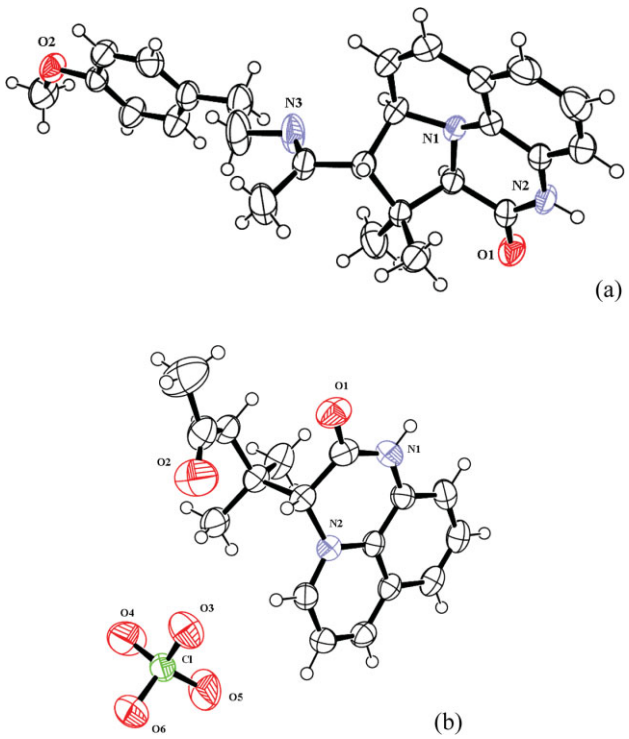
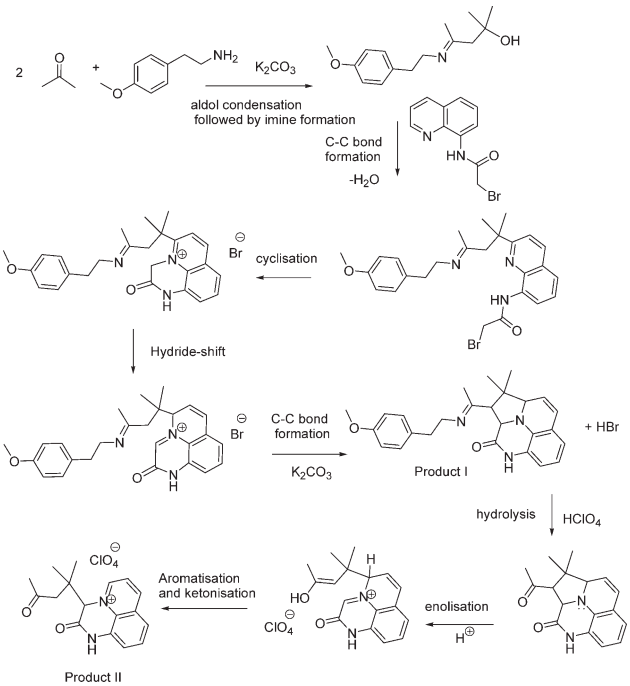
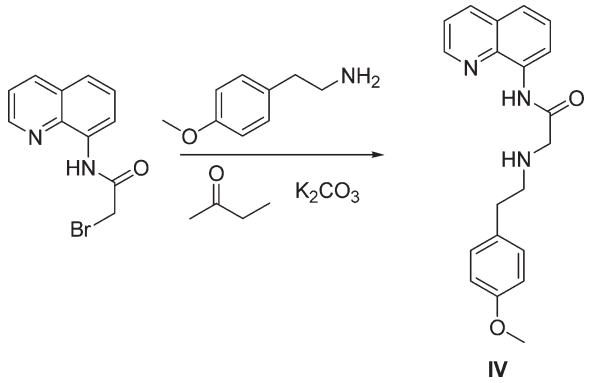


Figure 1. Crystal structure of (a) **I** and (b) **II** (ORTEP drawn with 50% thermal ellipsoid). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 2. Plausible paths for formation of **I** and **II**.



Scheme 3. Formation of product **IV** in ethyl methylketone.



IV

carbon. This new C—C bond formation along with enol to keto transformation as illustrated in Scheme 2 gives the final product **II**.

Furthermore, we did not observe any aldol condensation and cyclization reactions from the reaction between 2-bromo-*N*-quinoline-8-yl-acetamide and acetone in the presence of potassium carbonate without using an amine. When 2-(4-methoxyphenyl)ethylamine was reacted with acetone in the presence of potassium carbonate, it led to the corresponding imine. However, this imine did not react with 2-bromo-*N*-quinoline-8-yl-acetamide to give product **I**. This suggests that the aldol condensation and the formation of imine took place concomitantly in the presence of 2-bromo-*N*-quinoline-8-yl-acetamide. When the same reaction was carried out with 2-(2-methoxyphenyl)ethylamine, we obtained the product **III**. The formation of product, product **II** on treatment of **III** with perchloric acid, shows that formation of **II** does not depend on the amine used. The formation of a ketone instead of imine as the final product while using 2-(2-methoxyphenyl)ethylamine may be due to the hydrolysis of the corresponding imine. We also carried out similar reactions of 2-bromo-*N*-quinoline-8-yl-acetamide with other amines such as benzylamine, picolylamine, and no reaction was observed under analogous reaction conditions. However, aromatic amines such as 8-aminoquinoline replaced the bromide of 2-bromo-*N*-quinoline-8-yl-acetamide to form C—N bonded derivative. Use of ethylmethyl ketone as solvent did not lead to the aldol condensation reaction; instead, 2-(4-methoxyphynelamino)-*N*-(quinoline-8-yl)acetamide (**IV**) was formed by substitution of bromine by 2-(4-methoxyphenyl)ethylamine (Scheme 3).

In conclusion, these results demonstrate a new reaction leading to a novel heterocylic quinoxaline derivative **II**. The formation of compound **I** in one pot is advantageous, as synthesis of this compound by alternative routes would require multiple steps and less common reagents.

EXPERIMENTAL

Synthesis and characterization of compounds

Compound I. 2-Bromo-*N*-quinoline-8-yl-acetamide (1.4 g, 5 mmol), 2-(4-methoxyphenyl)ethylamine (0.735 mL, 5 mmol) and anhydrous potassium carbonate (1.03 g, 7.5 mmol) were added to dry acetone (20 mL), and the reaction mixture was stirred at 70°C for 12 h (progress of the reaction was monitored at regular intervals by using TLC). The reaction mixture was filtered to remove the residue and the solvent was removed under reduced pressure. The product obtained was purified by preparative thin layer chromatography using silica gel with 30% ethylacetate in petroleum ether as eluant. Yield: 41%. IR (KBr, cm^{-1}): 3125 (w), 3059 (m), 3008 (m), 2960 (m), 2923 (m), 1676 (s), 1658 (w), 1635 (m), 1613 (m), 1584 (m), 1511 (s), 1482 (s), 1387 (s), 1369 (w), 1270 (m), 1246 (s), 1172 (m), 1028 (m), 798 (m), 724 (m). ^{1}H NMR ($CDCl_3$): 8.4 (s, 1H), 7.1(d, J = 8.4 Hz, 2H), 6.8 (d, J = 6.4 Hz, 2H), 6.5 (m, 3H), 6.3 (d, J = 10 Hz, 1H), 5.7 (dd, J = 5.2, 10 Hz, 1H), 4.5 (dd, J = 5.2, 10 Hz, 1H), 3.7 (s, 3H), 3.53 (s,1H), 3.50 (t, J = 7.2 Hz, 2H), 2.8 (t, J = 7.2 Hz, 2H), 2.5 (d, J = 10.4 Hz,1H), 1.7 (s, 3H), 1.1 (s, 3H), 1.0 (s, 3H). ^{13}C NMR ($CDCl_3$): 20.3, 24.7, 27.1, 36.6, 44.6, 53.2, 55.5, 59.5, 66.4, 71.5, 109.9, 113.9, 114.6, 118.7, 120.3, 121.8, 123.5, 124.8, 125.2, 129.0, 130.0, 132.9, 158.1, 166.5. LC-MS [M^+] calcd for $C_{26}H_{29}N_3O_2$, 415.2260; found 415.2688.

Compound II. Compound **I** (0.41 g, 1 mmol) was dissolved in dilute perchloric acid (3*M*) and heated for 10 min. The solution was kept undisturbed, yellow colored crystal of compound **II** appeared after 6 days. Yield: 46%. IR (KBr, cm^{-1}): 3258 (m), 3110 (w), 3083 (m), 2962 (m), 1705 (s), 1608 (w), 1587 (m), 1541 (s), 1471 (m), 1427 (s), 1384 (m), 1361(m), 1239 (w), 1177 (m), 1100 (s), 927 (m), 839 (s), 764 (m), 623 (s). ^{1}H NMR ($CDCl_3$/DMSO-d_6): 12.0 (s,1H), 9.4 (d, J = 6 Hz, 1H), 9.2 (d, J = 8.4 Hz, 1H), 8.2 (m, 1H), 8.0 (d, J = 8.4 Hz, 1H), 7.9 (t, J = 8.0 Hz, 1H), 7.6 (d, J = 7.6 Hz, 1H), 6.0 (s, 1H), 2.9 (d, J = 18.4 Hz, 1H), 2.6 (d, J = 19.2 Hz, 1H), 2.1 (s, 3H), 1.0 (s, 3H), 0.7 (s, 3H). ^{13}C NMR (DMSO-d_6): 24.0, 24.7, 31.5, 51.2, 72.9, 118.9, 122.9, 123.2, 127.3, 129.8, 131.0, 131.5, 148.3, 149.8, 162.1, 206.9. LC-MS [M^+] calcd for $C_{17}H_{19}N_2O_2ClO_4$, 283.1441; found 283.1651.

Compound III. 2-Bromo-*N*-quinoline-8-yl-acetamide (1.4 g, 5 mmol), 2-(2-methoxyphenyl)ethylamine (0.735 mL, 5 mmol) and anhydrous potassiumcarbonate (1.03 g, 7.5 mmol) were added to dry acetone (20 mL) and the reaction mixture was stirred at 70°C for 12 h (progress of the reaction was monitored at regular intervals using TLC). The reaction mixture was filtered to remove the residue and the solvent was removed under reduced pressure. The product obtained was purified by preparative thin layer chromatography using silica gel with 30% ethylacetate in petroleum ether as eluant. Yield: 25%. IR (KBr, cm^{-1}): 3432 (b), 2924 (s), 2853 (m), 1681 (s), 1596 (m), 1527 (s), 1491 (m), 1458 (m), 1384 (m), 1325 (m), 1244 (s), 1174 (w), 1024 (m), 827 (m), 792 (m), 753 (s). ^{1}H NMR ($CDCl_3$): 8.2 (s, 1H), 6.4 (m, 2H), 6.3 (d, J = 7.2 Hz, 1H), 6.1 (d, J = 10 Hz, 1H), 5.5 (m, 1H), 4.1 (m, 1H), 3.3 (s, 1H), 2.6 (d, J = 10 Hz, 1H), 1.9 (s, 3H), 0.9 (s, 6H). ^{13}C NMR (CDCl3): 24.7, 26.9, 33.1, 45.3, 59.8, 68.6, 71.3, 114.8, 116.7, 119.1, 120.7, 122.1, 123.3, 136.3, 148.7, 165.5. LC-MS [M^+] calcd for $C_{17}H_{18}N_2O_2$, 282.1368; found 283.1448 [M^++1].

Compound IV. 2-Bromo-*N*-quinoline-8-yl-acetamide (1.4 g, 5 mmol), 2-(4-methoxyphenyl)ethylamine (0.735 mL, 5

mmol), and anhydrous potassiumcarbonate (1.03 g, 7.5 mmol) were added to ethyl methylketone (20 mL), and the reaction mixture was stirred at 70°C for 12 h (progress of the reaction was monitored at regular intervals using TLC). The reaction mixture was filtered to remove the residue and the solvent was removed under reduced pressure. The product obtained was purified by preparative thin layer chromatography using silica gel with 30% ethylacetate in petroleum ether as eluant. Yield: 45%. IR (KBr, cm^{-1}): 3315 (m), 2925 (m), 2851 (w), 1655 (s), 1612 (w), 1579 (w), 1530 (s), 1488 (m), 1463 (m), 1424 (w), 1326 (s), 1245 (s), 1175 (m), 1033 (m), 786 (s), 750 (m). ^{1}H NMR ($CDCl_3$): 10.5 (s, 1H), 8.7 (m, 2H), 8.1 (d, J = 6.8 Hz, 1H), 7.5 (m,3H), 7.4 (q, J = 4 Hz, 1H), 7.1 (d, J = 8.4, 1H), 6.8 (d, J = 8.8, 1H), 4.3 (s, 3H), 3.7 (s,2H), 3.5 (s, 1H), 2.9 (t, J = 6.8 Hz, 2H), 2.8 (t, J = 6.0 Hz, 2H). ^{13}C NMR (DMSO-d_6/$CDCl_3$): 28.8, 34.9, 62.0, 85.4, 115.5, 121.1, 121.2, 126.4, 127.3, 129.0, 133.3, 135.6, 137.6, 147.8, 170.6. LC-MS [M^+] calcd for [M^+] $C_{20}H_{21}N_3O_2$, 335.1634; found 336.1679 [M^++1].

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