SYNTHESIS OF $N$-HETEROPOLYCYPICAL COMPOUNDS INCLUDING QUINAZOLINONE SKELETON USING FRIEDEL-CRAFTS ALKYLATION

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GRAPHICAL ABSTRACT

Abstract A simple method to synthesize $N$-heteropolycyclic quinazolinones was developed including Knoevenagel condensation of quinazolines and aldehydes and Friedel–Craft alklylation as key steps. Knoevenagel reaction of 2-methyl-3-phenylquinazolin-4(3H)-one proceeded smoothly under a basic condition and subsequent Friedel–Craft alklylation with Brønsted acid gave the $N$-heteropolycyclic quinazolinones in good yields. Furthermore, these new polycyclic compounds were converted into organic molecules having a long $\pi$-conjugation system by treatment of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to utilize them as organic dyes.

Keywords Friedel–Crafts alklylation; Knoevenagel condensation; $N$-heteropolyccycle; quinazolinone

INTRODUCTION

Quinazolinone derivatives are one of valuable heterocyclic compounds in medical chemistry because of their various biological and pharmaceutical activities\[1\] including antihypertensive,\[2\] antidepressant,\[3\] anticonvulsant,\[4\] anticancer,\[5\] and anti-inflammatory\[6\] activities. It has also been attracted much attention in organic synthesis because natural products such as methaqualone,\[7\] luotonins A,\[8\] mackinazoline,\[9\] sclerotigenin,\[10\] rutaecarpine,\[11\] and tryptanthrin\[12\] are able to be synthesized from the quinazolinone skeleton (Fig. 1). In addition, quinazolinone
compounds containing a long π-electron conjugated moiety have been used as organic dyes.\textsuperscript{[13]}

In previous research, a lot of synthetic methods have been reported for quinazolinone derivatives: iodine-catalyzed condensation of anthranilamide and aldehydes in ionic liquid,\textsuperscript{[14]} domino reaction of amino acids and benzamides by copper catalyst,\textsuperscript{[15]} multicomponent reaction of benzyl halides, amines, and isatoic anhydride,\textsuperscript{[16]} cyclocondensation of anthranilamide and aldehydes in the presence of cyanuric chloride,\textsuperscript{[17]} palladium-catalyzed benzylic C–H activation from benzyl alcohol and aminobenzamides,\textsuperscript{[18]} EDC-amide coupling of benzoic acids and anilines,\textsuperscript{[19]} and conversion of benzoic acids into benzoyl chlorides and amine by using Vilsmeier reagent.\textsuperscript{[20]} In this communication, we report a synthetic methodology to prepare more complicated heteropolycyclic compounds containing the quinazolinone moiety, 5-substituted-12\textit{H}-quinolino[2,1-\textit{b}]quinazolin-12-ones (1a–e) from 2-methyl-3-phenylquinazolin-4(3\textit{H})-one derivatives (4a,b) (Scheme 1).
RESULTS AND DISCUSSION

We prepared a starting quinazolinone substrate (4a,b) from 2-nitrobenzoic acid (5a,b) via the following synthetic routes. At first, 5a,b was converted into 2-nitrobenzoyl chloride by oxalyl chloride, and a catalytic amount of N,N-dimethylformamide (DMF) in dichloroethane (DCE) and subsequent treatment of aniline gave the amide coupling product. After a reduction in the presence of palladium-charcoal catalysts under a hydrogen atmosphere, the amine product 6a,b was obtained in good yield. Finally, the acetylated product 7a,b was converted into 4a,b (Scheme 2) without any difficulties.

Because the proton in 2-methyl group of 2-methyl-3-phenylquinazolin-4(3H)-one (4a) known to be relatively acidic forms carbanion species easily, many reactions, such as alkylation, sulfenylation, aldol condensation, and acylation, have been reported in the literature.[21] Utilizing this property, we planned a synthetic route to prepare heteropolycyclic systems, that is, Knoevenagel condensation[22] of quinazolinone derivatives and aldehydes, followed by Friedel–Crafts alkylations[23] (Scheme 3).

From the quinazolinone substrate (4) and aldehydes, the condensation product 3 was prepared in good yields by Knoevenagel reactions. The reaction proceeded smoothly in quite simple acidic or basic conditions. Various internal alkanyl products 3 having different electronic properties were synthesized under acidic conditions (Scheme 4).

With these Knoevenagel condensation products (3a–e), we tried to synthesize cyclization products by Friedel–Crafts reaction. The reaction conditions were screened with a quinazolinone 3c to optimize Brønsted acids or Lewis acids, solvents, and temperatures (Table 1). Because of a harsh condition without solvent, methanesulfonic acid (MeSO3H), the reaction resulted in a lower yield (entry 1). A reduced amount of MeSO3H in dichloroethene (DCE) gave good results at both 120 °C and 150 °C, but reaction time was long (entries 2 and 3). Eventually, trifluoromethanesulfonic acid

![Scheme 2](image)

**Scheme 2.** Reagents and conditions: (a) (1) oxalyl chloride, DMF (cat.), DCE, rt, 2 h, and then pyridine, aniline, DCE, rt, 8 h; (2) H2 (1 atm), Pd/C, ethanol, rt, 4 h, 6a: 88%, 6b: 85%; (b) Et3N, acetic anhydride, CH2Cl2, 40 °C, 2 h, 7a: 90%, 7b: 88%; (c) Et3N, TMSCl, DCE, 100 °C (reflux), 3 h, 4a: 88%, 4b: 87%.

![Scheme 3](image)

**Scheme 3.** Synthetic strategy for heteropolycyclic compounds.
(CF₃SO₃H) was found to be the best acid in our reaction conditions (entry 4). Phosphoric acid (H₃PO₄) afforded cyclization product in 50% yield (entry 5). Lewis acids, such as AlCl₃, FeCl₃, BF₃•OEt₂, and TiCl₄ were not effective acid for this reaction (entries 6–9).

Table 1. Cyclization of 3c under various acid conditions

| Entry | Acid          | Solvent | Temp. (°C) | Time (h) | Yield (%) |
|-------|---------------|---------|------------|----------|-----------|
| 1     | MeSO₃H (100 eq) | DCE     | 150        | 4        | 42        |
| 2     | MeSO₃H (5 eq)   | DCE     | 120        | 12       | 66        |
| 3     | MeSO₃H (5 eq)   | DCE     | 150        | 6        | 62        |
| 4     | CF₃SO₃H (5 eq)   | DCE     | 100        | 4        | 76        |
| 5     | H₃PO₄ (5 eq)    | DCE     | 150        | 4        | 50        |
| 6     | AlCl₃(3 eq)     | DCE     | 150        | 12       | Trace     |
| 7     | FeCl₃(3 eq)     | DCE     | 150        | 12       | Trace     |
| 8     | BF₃•OEt₂ (3 eq) | Toluene | 150        | 12       | Trace     |
| 9     | TiCl₄(3 eq)     | Toluene | 150        | 12       | Trace     |

Reactions were performed with 3c (0.1 mmol) in solvent (0.25 M).

Isolated yield.
With these optimized conditions in hands, we were able to synthesize polycyclic compounds 2 containing quinazolinone skeleton (Scheme 5) for application to organic dyes.

Because 2 did not have a fully conjugated π system, we tried to convert them into 1 by aromatization. Thus, the fully conjugated product 1 was successfully synthesized by treatment of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with 2 (Scheme 6).

**Scheme 5.** Intramolecular Friedel–Crafts cyclizations of 3a–e.

**Scheme 6.** Aromatization of 2a–e by DDQ reagent.
More complicated compounds 8 having longer π conjugation were also synthesized utilizing palladium-catalyzed cross-coupling reactions. For example, 1c was reacted with o-tolylboronic acid and styrene to give the corresponding cross-coupling product 8a and 8b, respectively (Scheme 7) in good yields.

CONCLUSIONS

In summary, we developed a methodology to produce heteropolycyclic compounds by simple Friedel–Crafts alkylation of quinazolinone derivatives. The fully conjugated quinazolinone derivatives are anticipated to be utilized as organic dyes. Spectroscopic analyses of our heteropolycyclic compounds are now in progress.

EXPERIMENTAL

Synthesis of (E)-2-(4-Bromostyryl)-3-phenylquinazolin-4(3H)-one (3c)

Under an Ar atmosphere 2-methyl-3-phenylquinazolin-4(3H)-one (4a) (500 mg, 2.1 mmol), 4-bromobenzaldehyde (590 mg, 3.2 mmol), and sodium acetate (340 mg, 4.2 mmol) were dissolved in glacial acetic acid (8 mL) at 0 °C. The reaction mixture was heated for 8 h at 150 °C. The crude reaction mixture was cooled to 0 °C and poured into crushed ice. The precipitate was collected by filtration, washed with water, and recrystallized from ethyl acetate and hexane to give a product (650 mg, 77%) as a yellow solid. 3c: mp 212 – 213 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.82–7.79 (m, 2H), 7.62–7.52 (m, 3H), 7.51–7.47 (m, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.2 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.37 (d, J = 15.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 162.34, 151.51, 147.79, 138.60, 136.97, 134.69, 134.29, 132.11, 130.08, 129.55, 129.23, 128.78, 127.40, 127.30, 126.89, 123.89, 121.06, 120.63, 120.61; IR (NaCl, cm⁻¹) 3059, 1681, 1632, 1548. HRMS (ESI) calcd. for (C₂₂H₁₄N₂O + Na)⁺ requires m/z 425.0260; found m/z 425.0260.
Synthesis of 5-(4-Bromophenyl)-5,6-dihydro-12H-quinolino[2,1-b]quinazolin-12-one (2c)

Under an Ar atmosphere (E)-2-(4-bromostyryl)-3-phenylquinazolin-4(3H)-one (3c) (400 mg, 1.0 mmol) and trifluoromethanesulfonic acid (0.4 mL, 5.0 mmol) were diluted in DCE (4 mL) at 0 °C. The reaction mixture was heated for 8 h at 100 °C. The crude mixture was diluted with water, extracted with ethyl acetate, and washed with NaHCO₃ and NaCl solution. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The concentrated residue was purified by flash silica-gel chromatography by using a 1:2 mixture of ethyl acetate/hexane to give a product (280 mg, 71%) as a white solid. 2c: mp 182–184 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.45–7.40 (m, 3H), 7.27 (t, J = 8.0 Hz, 1H), 7.09–7.03 (m, 3H), 4.30 (t, 6.0 Hz, 1H), 3.46–3.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 160.72, 152.92, 146.21, 138.36, 134.72, 134.29, 133.56, 132.15, 129.57, 127.87, 127.63, 127.57, 127.33, 126.98, 126.73, 124.48, 122.01, 121.38, 40.98, 40.37; IR (NaCl, cm⁻¹) 3064, 1686, 1595; HRMS (ESI) calcd. for (C₂₂H₁₅BrN₂O + Na)⁺ requires m/z 425.0260; found m/z 425.0260.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.
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