Copper–phenanthroline catalysts for regioselective synthesis of pyrrolo[3′,4′:3,4]pyrrolo[1,2-a]furoquinolines/phenanthrolines and of pyrrolo[1,2-a]phenanthrolines under mild conditions

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Abstract
A new series of pyrrolo[3′,4′:3,4]pyrrolo[1,2-a]furoquinolines/phenanthrolines and pyrrolo[1,2-a]phenanthrolines were efficiently built up from an 8-hydroxyquinoline derivative or phenanthroline via 1,3-dipolar cycloaddition reaction involving non-stabilized azomethine ylides, generated in situ from the parent furo[3,2-h]quinoliniums/phenanthroliniums, in presence of a copper(II) chloride–phenanthroline catalytic system. The methodology combines general applicability with high yields.

Introduction
The chemistry of the 1,3-dipolar cycloaddition has always been a fascinating undertaking especially when azomethine ylides are involved as the key component [1-9]. These ylides, both stabilized or non-stabilized 1,3-dipoles, can easily enter the reaction independent of their stability and lead to the formation of a pyrrolidine core, a structural motif of immense interest from both chemical and pharmacological points of view [10]. In recent years, there have been many attempts to synthesize diversely modified pyrrolidines, both symmetric and asymmetric in nature. Several of these attempts involved 1,3-dipolar cycloaddition reactions involving azomethine ylides to give cycloadducts, which were further explored as potential antiviral, antifungal, antitumor and anti-HIV candidates [1-15]. We have also been pursuing the cycloaddition methodology...
for several years and established some synthetic routes towards indolizines, pyrrolo[1,2-a]quinolines/isoquinolines, oxazadicyclopenta[a,h]napthalenes etc., some of which have been evaluated as potential antibacterial and antifungal agents [16-19]. In order to explore the possibility of using structurally more complex dipoles and dipolarophiles to construct more interesting structural networks, we replaced simple alkenes/alkynes with maleimide derivatives. Our preference for this dienophile was dictated by a recent patent on the lifespan altering properties of cycloadducts involving maleimide dienophiles [20]. Moreover, very recently we have characterized some furo[3,2-h]quinoliniums as potent non-detergent spermicides [19], which encouraged us for further modification and derivatization of furoquinoline analogues in search for more potent agents. Thus we became interested in the construction of a number of structurally complex pentacyclic pyrrolo[3′,4′:3,4]pyrrolo[1,2-a]furoquinolines, for possible identification of new antibacterial/antifungal/spermicidal/lifespan altering agents, where furo[3,2-h]quinoliniums were employed as dipole precursors and maleimide derivatives as dipolarophiles.

We initially employed the protocols from our recently developed green methodologies [21-25], which however failed to give any promising outcome and forced us to explore new catalytic systems. While searching for this goal, we were attracted by the possible application of copper-catalysis, which has always been an effective tool especially with Diels–Alder reactions [26,27]. Thus, we studied the effect of a number of catalytic systems and after an extensive screening, we found copper(II) chloride–phenanthroline as the best catalytic pair for this purpose. Herein we wish to present the results of our recent synthetic efforts to synthesize a series of unique pentacyclic pyrrolo[3′,4′:3,4]pyrrolo[1,2-a]furoquinolines/phenanthrolines using the above catalytic system. To the best of our knowledge, this is the first report of the application of this catalyst for the regioselective 1,3-dipolar cycloaddition reaction, involving azomethine ylides derived from structurally complex quinoline-based N-heterocycles.

Results and Discussion
Our studies started with the preparation (Scheme 1 and Scheme 2) of maleimides 4a–c employing maleic anhydride (1) and different aromatic amines 2a–c, and of furo[3,2-h]quinoliniums 9a–d from 5-chloro-8-hydroxy-7-iodoquinoline 5 [19,24]. However, attempted condensation of 4a with the 1,3-dipole generated in situ from 9a, employing protocols from our
recently developed methodologies, did not succeed, affording products only in low yields (10–19%, Table 1, entries 1–7). We then studied the feasibility of a metal-catalyzed 1,3-dipolar cycloaddition strategy. A thorough screening of different catalysts, as summarized in Table 1, revealed the supremacy of copper catalysts in this particular reaction over the others; CuCl₂ appeared to be the catalyst of choice (Table 1, entries 8–32). In order to explore the effect of ligands, a number of phosphines, bis-oxazocines, pyrazolyl-pyrimidines and phenanthroline analogues were employed (Figure 1). As represented in Table 1, the monodentate ligands are in general less effective

| Entry | Catalytic system | Solvent | Time (h) | Temp. (°C) | Yield |
|-------|-----------------|---------|----------|------------|-------|
| 1     | Basic alumina   | None    | 0.3      | 80         | 10c   |
| 2     | Amberlite IRA 402 (OH) | H₂O   | 10       | 90         | 16    |
| 3     | K-10 clay       | None    | 0.3      | 80         | 12c   |
| 4     | Triton X-114 (60 mM) | H₂O   | 3        | rt         | 17    |
| 5     | SDS (60 mM)     | H₂O     | 3        | rt         | 15    |
| 6     | TTAB (80 mM)    | H₂O     | 6        | rt         | 19    |
| 7     | CTAB (90 mM)    | H₂O     | 5        | rt         | 12    |
| 8     | SnCl₂           | Toluene | 8        | 80         | NR    |
| 9     | Sc(OTf)₃       | DCM     | 10       | rt         | NR    |
| 10    | Sc(OTf)₃       | Toluene | 10       | 80         | NR    |
| 11    | Mg(ClO₄)₃      | DCM     | 10       | rt         | NR    |
| 12    | Mg(ClO₄)₃      | Toluene | 10       | 80         | 11    |
| 13    | Cu(OTf)₂       | DCM     | 8        | rt         | 15    |
| 14    | Cu(OTf)₂       | Toluene | 8        | 80         | 28    |
| 15    | Cu(OAc)₂       | DCM     | 8        | rt         | 12    |
| 16    | Cu(OAc)₂       | Toluene | 8        | 80         | 32    |
| 17    | Cu(OAc)₂       | MeCN    | 8        | 65         | 47    |
| 18    | CuCl₂          | DCM     | 6        | rt         | 23    |
| 19    | CuCl₂          | Toluene | 6        | 80         | 45    |
| 20    | CuCl₂          | MeCN    | 3        | 65         | 57    |
| 21    | CuCl₂/PPh₃     | MeCN    | 3        | 65         | 58    |
| 22    | CuCl₂/PMePh₂   | MeCN    | 3        | 65         | 58    |
| 23    | CuCl₂/PCy₃     | MeCN    | 3        | 65         | 56    |
| 24    | CuCl₂/P(3-ClC₆H₄)₃ | MeCN | 3        | 65         | 58    |
| 25    | CuCl₂/P(3-OHMeC₆H₄)₃ | MeCN | 3        | 65         | 55    |
| 26    | CuCl₂/DPEphos  | MeCN    | 3        | 65         | 65    |
| 27    | CuCl₂/xantphos | MeCN    | 3        | 65         | 67    |
| 28    | CuCl₂/pyphos   | MeCN    | 3        | 65         | 65    |
| 29    | CuCl₂/oxazocine| MeCN    | 3        | 65         | 74    |
| 30    | CuCl₂/pyrimidine| MeCN   | 3        | 65         | 71    |
| 31    | CuCl₂/phenanthroline (L₁) | MeCN | 3        | 65         | 94    |
| 32    | CuCl₂/phenanthroline (L₂) | MeCN | 3        | 65         | 94    |

Notes: All the reactions were performed in presence of DBU; Isolated yield; The reactions were performed under microwave irradiation at 180 W.
Figure 1: Bi-/tridentate ligands used for the optimization of the reaction conditions.

Figure 2: ORTEP diagram showing the molecular structure of 10a at 30% probability level.

The plausible mechanism of this cycloaddition is presented in Scheme 3. The base (DBU) abstracts the acidic proton of furo[3,2-\(h\)]quinolinium 9a to generate the 1,3-dipole I. The Cu(II)–phenanthroline system activates the maleimide dipolarophile via coordination with the carbonyl group to undergo a [3 + 2] cycloaddition with the 1,3-dipole to form the cycloadduct 10a, releasing the Cu(II) complex to enter another cycle.

In order to establish the general applicability of this protocol, we reacted different furo[3,2-\(h\)]quinoliniums 9a–d and maleimide dipolarophiles 4a–c under the standardized reaction conditions. As obvious from the results summarized in Scheme 4, all the reactions proceeded smoothly to give cycloadducts with excellent yields, which were fully characterized by mass and NMR analysis.

In order to test its general applicability further, we replaced furo[3,2-\(h\)]quinoliniums 12a,b with alkylene dipolarophiles like acetylenedicarboxylates or monocarboxylates 13a–d with alkylene dipolarophiles like acetylenedicarboxylates or monocarboxylates 13a–d proceeded with aromatization of the putative dihydroaromatic intermediates to produce the final cycloaddition products 14d–g.

Characterization of the products was done via mass and NMR spectral studies. Furthermore, the single-crystal X-ray study of 10a confirmed the structure of the cycloadduct 10a.
cycloadduct 14e undoubtedly confirmed the structure of these cycloadducts, as obvious from the ORTEP diagram presented in Figure 3.

Conclusion
In conclusion, a simple CuCl$_2$-phenanthroline catalyzed methodology has been developed to synthesize a series of unique heteroaromatic polycycles 10a–h, 14a–g by a 1,3-dipolar cycloaddition reaction, using furo[3,2-h]quinolinium/phenanthrolinium dipole precursors and maleimide/acytylene-carboxylate dipolarophiles. High atom-economy, good to very good isolated yield of the products, short reaction time and ease of separation coupled with general applicability are the key features of this methodology.

Experimental
General procedure to synthesize pyrrolo[3′,4′:3,4]pyrrolo[1,2-a]furoquinolines 10a–h, pyrrolo[3′,4′:3,4]pyrrolo[1,2-a]phenanthrolines 14a–c, and pyrrolo[1,2-a]phenanthrolines 14d–g: A mixture of 3.3 mmol furo[3,2-h]quinolinium derivatives 9a–d/phenanthroliniums 12a,b and 3.3 mmol N-phenylmaleimide derivatives 4a–d/dialky acetylenedicarboxylates 13a–b/monoalkyl acetylend monocarboxylates 13c,d was placed in a round bottomed flask (25 mL). To this MeCN (50 mL) and DBU (1 mmol) were added and the mixture was stirred for 30 min. Then 5 mol % CuCl$_2$ and 5 mol % of either L$_1$, L$_2$ were added to the reaction mixture and stirred continuously for 3 h at 65 °C. After completion of the reaction (monitored by TLC), the reaction mixture was partitioned between brine and ethyl acetate. The organic layer was then evaporated and purified by column chromatography (ethyl acetate:hexane).

NMR data and crystal data of some representative compounds: a) spectral data of 10a: Yellow solid. 94% yield; mp 246–248 °C; $R_f$ (20% ethyl acetate–hexane) 0.35; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.65 (t, $J$ = 8.1 Hz, 1H), 3.84 (s, 3H), 3.89 (m, 1H), 5.52 (m, 1H), 6.18 (m, 1H), 6.64 (s, 1H), 6.76 (s, 1H), 6.98 (m, 8H), 7.11 (m, 1H), 7.20 (m, 2H), 7.65 (t, $J$ = 7.5 Hz, 2H), 7.76 (d, $J$ = 7.2 Hz, 1H), 8.48 (d, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 47.2 (CH), 47.4 (CH), 55.5 (CH$_3$), 61.0 (CH), 66.5 (CH), 101.6 (CH), 110.8 (CH), 114.5 (2CH), 116.0 (C), 119.7 (CH), 124.0 (CH), 124.6 (2CH), 127.6 (2CH), 127.6 (C), 128.4 (3CH), 128.4 (C), 128.8 (C), 129.3 (C), 129.4 (2CH), 129.6 (2CH), 131.2 (C), 133.1 (C), 134.4 (CH), 140.6 (C), 157.0 (C), 159.8 (C), 174.9 (C), 176.6 (C), 194.5 (C); HRMS (ESI) m/z: [M + Na]$^+$ calcld for C$_{36}$H$_{25}$CIN$_2$NaO$_5^+$ 623.1344; found, 623.1353. b) Spectral data of 14a: Yellow solid. 81% yield; mp 242–243 °C; $R_f$ (20% ethyl acetate–hexane) 0.31; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.26 (s, 6H), 3.65 (m, 1H), 3.74 (m, 1H), 5.94 (m, 1H), 6.18 (m, 1H),...
Scheme 4: Synthesis of pyrrolo[3′,4′:3,4]pyrrolo[1,2-a]furoquinoline analogues under the optimized protocol.

6.54 (m, 1H), 7.00 (m, 3H), 7.07 (m, 2H), 7.19 (m, 2H), 7.64 (m, 4H), 7.85 (m, 1H), 8.33 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 19.5 (CH$_3$), 19.7 (CH$_3$), 46.9 (CH), 47.5 (CH), 63.4 (CH), 67.0 (CH), 116.9 (CH), 120.4 (CH), 121.1 (C), 121.6 (C), 123.7 (CH), 126.4 (CH), 126.9 (CH), 127.3 (CH), 128.2 (C), 128.7 (2CH), 128.8 (2CH), 129.1 (C), 129.4 (C), 130.2 (CH), 132.9 (CH), 134.6 (C), 136.0 (CH), 137.7 (C), 137.9 (C), 138.5 (C), 145.3 (CH), 175.7 (C), 176.9 (C), 196.6 (C); HRMS (ESI) $m/z$: [M + Na]$^+$ calcld for C$_{32}$H$_{25}$N$_3$NaO$_3^+$ 522.1788; found, 522.1799. c) Spectral data of 14e: Brown solid. 91% yield; mp 233–234 °C; $R_f$ (20% ethyl acetate–hexane) 0.33; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.06 (t, $J$ = 7.2 Hz, 3H), 1.38 (t, $J$ = 7.2 Hz, 3H), 3.72 (m, 1H), 3.88 (m, 1H), 4.38 (m, 2H), 7.33 (m, 1H), 7.51 (t, $J$ = 7.4 Hz, 2H), 7.60 (m, 1H), 7.69 (d, $J$ = 9.3 Hz, 1H), 7.83 (m, 2H), 8.01 (m, 1H), 8.17 (d, $J$ = 7.8 Hz, 3H), 8.57 (d, $J$ = 9.3 Hz, 1H); $^{13}$C NMR (75 MHz,
CDCl$_3$ δ 13.6 (CH$_3$), 14.3 (CH$_3$), 60.4 (CH$_2$), 61.4 (CH$_2$), 104.0 (C), 120.2 (CH), 122.5 (CH), 125.3 (CH), 125.6 (C), 126.8 (C), 126.0 (CH), 126.7 (CH), 127.7 (C), 128.1 (2CH), 129.0 (C), 130.0 (2CH), 130.7 (C), 132.2 (CH), 135.9 (CH), 137.3 (C), 137.4 (C), 137.9 (C), 145.7 (CH), 163.5 (C), 163.5 (C), 184.4 (C); HRMS (ESI) m/z: [M + Na]$^+$ calc'd for C$_{28}$H$_{22}$N$_2$O$_5$+ 489.1421; found, 489.1437.

d) Crystal data for 10a: C$_{36}$H$_{25}$N$_2$Cl, M = 601.03 , monoclinic, P2$_1$/c, a = 15.687(2), b = 19.297(2), c = 9.848(1) Å, β = 99.476(8)°, V = 2940.5(7) Å$^3$, Z = 4, D$_c$ = 1.358 g cm$^{-3}$, μ = 0.094 mm$^{-1}$, F$_{000}$ = 976, λ (Mo Kα) = 0.71073 Å, yellowish block, crystal size: 0.17 × 0.11 × 0.09 mm, 25248 reflections measured (R$_{int}$ = 0.0552), 3534 unique reflections, wR(F$^2$) = 0.1976 for all data and conventional R = 0.0501 for 2741 F-values with l>2σ(l), (Δ/σ)$_{max}$ = 0.000, S = 1.504 for all data and 319 parameters, Δρ$_{max}$, min (e/Å$^3$) = 0.267, −0.351.

e) Crystal data for 13f: C$_{28}$H$_{22}$N$_2$O$_5$, M = 466.48 , monoclinic, P2$_1$/c, a = 11.9769(8), b = 17.281(1), c = 11.6975(8) Å, β = 109.484(3)°, V = 2282.4(3) Å$^3$, Z = 4, D$_c$ = 1.358 g cm$^{-3}$, μ = 0.094 mm$^{-1}$, F$_{000}$ = 976, λ (Mo Kα) = 0.71073 Å, yellowish block, crystal size: 0.17 × 0.11 × 0.09 mm, 25248 reflections measured (R$_{int}$ = 0.0552), 3534 unique reflections, wR(F$^2$) = 0.1976 for all data and conventional R = 0.0501 for 2741 F-values with l>2σ(l), (Δ/σ)$_{max}$ = 0.000, S = 1.504 for all data and 319 parameters, Δρ$_{max}$, min (e/Å$^3$) = 0.267, −0.351.

Unit cell determinations and intensity data collections for both
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 Supporting Information

Supporting Information File 1
Experimental and analytical data and copies of 1H NMR and 13C NMR spectra of all new products.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-62-S1.pdf]
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