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A Novel Synthesis of 2-(2-Quinoxalino)-3,5-diarylfurans

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Abstract: A short synthesis of 2-(2-quinoxalino)-3,5-diarylfurans, allowing the stepwise introduction of the aromatic rings, is designed and implemented utilizing the DDQ promoted cyclization of 4-(2-quinoxalino)-1,3-diarylbutanones as the key transformation.

Keywords: furans; cyclization; oxidation; x-ray crystal structure; quinoxalines

The furan ring system is found in many natural products and pharmaceutical agents either unsaturated or in a partly or fully reduced state. Many simple furan derivatives may be prepared from commercially available furans such as furfural (furan-2-carboxaldehyde) however for more complex substitution patterns acyclic precursors are usually involved.[1] Classical furan syntheses include the acid-catalyzed cyclization of 1,4-dicarbonyl compounds (the Paal-Knorr synthesis[2]) or the cyclo-condensation of an α-haloketone with a 1,3-dicarbonyl compound (the Feist-Benary synthesis.[3]) Other methods include oxidative cyclization of cis-1,4-butenediols[4] or 1,3-dipolar-cycloadditon reactions of carbonyl ylides.[5] While these methods have many successful examples they mostly suffer from the harsh conditions involved and the lack of appropriately functionalized, commercially available precursors. In this letter we disclose the synthesis of triaryl-substituted furans by the oxidative cyclization of triarylbutanones under mild conditions. Of most importance is the ability to install all three aryl rings of the triarylbutanone precursors independently in a step-wise fashion resulting in increased ease of diversity introduction. This approach lends itself well to the rapid, parallel production of arrays of diversely-substituted furans.

The strategy for the present synthesis is outlined in Scheme 1. It was anticipated that an appropriate α-methyl nitrogen heterocycle **1** would condense with an aryl aldehyde and the resulting styrene derivative **2** would act as a Michael acceptor for arylmethylketones affording the triarylbutanones **3**. It was then hoped that the triarylbutanones would cyclize under oxidative conditions to afford the triarylfuran targets **4**. Initially, 3-methylquinoxaline-2-ones were chosen as representative α-methyl nitrogen heterocycles since their

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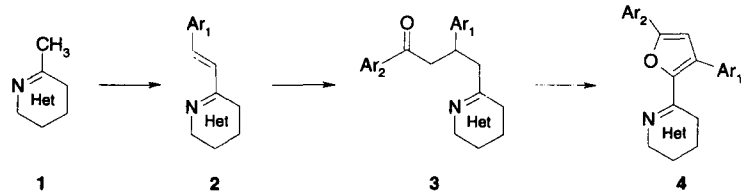
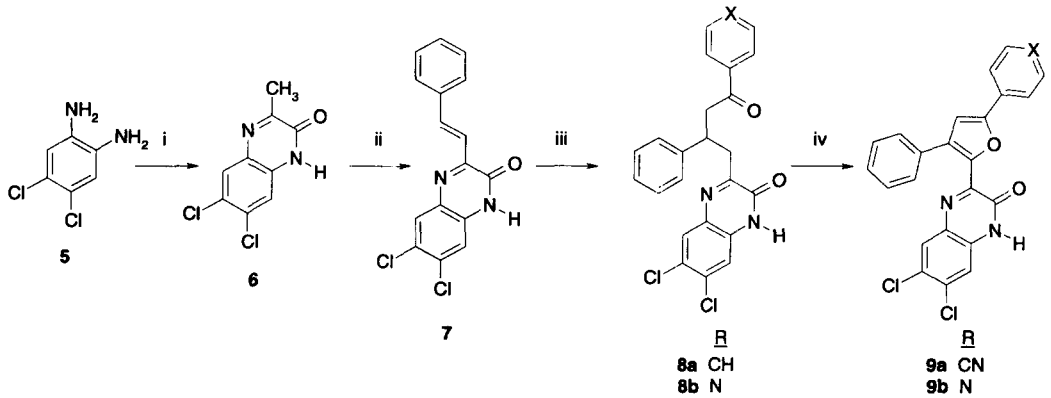


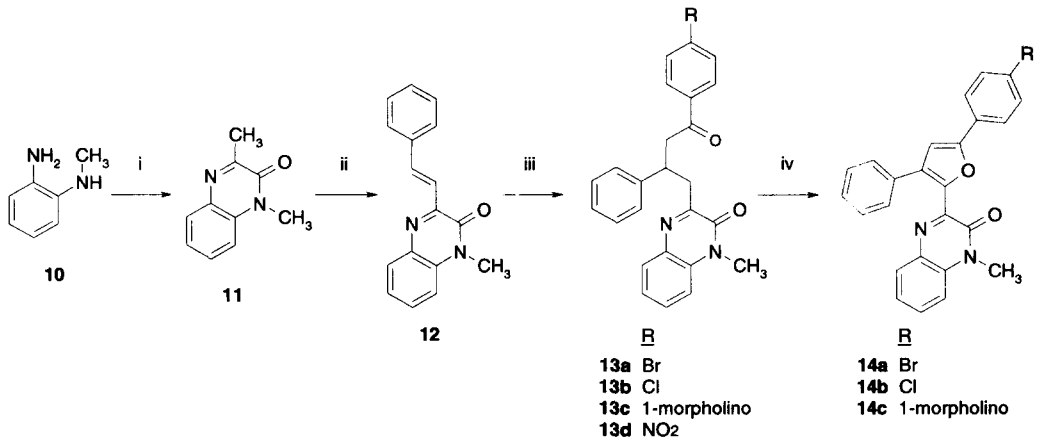
Scheme 1

condensation with aryl aldehydes has been studied.[6] 3-Methyl-6,7-dichloroquinoxalin-2-one **6** was prepared (Scheme 2) from the requisite phenylenediamine **5** in 96% yield and its condensation with benzaldehyde examined. Under standard conditions (piperidine, acetic acid, toluene, reflux, removal of water) only starting material was recovered most likely due to the low solubility of **6** in non-polar solvents. However, by using dimethylformamide (DMF) as solvent and NaH as base, the desired condensation product **7** could be obtained in 49% yield and could be carried out on a large scale (>10 g). Base-catalyzed addition of acetophenone and 4-acetylpyridine then provides ketones **8a** (55%) and **8b** (83%) respectively. Treatment of **8a** with two equivalents of DDQ in refluxing 1,2-dichloroethane resulted in complete conversion to a new compound (33% isolated yield after chromatography). Mass spectral and combustion analysis suggested the formula $C_{24}H_{14}Cl_2N_2O_2$ for the product and that a double oxidation had occurred which is consistent with the need for two equivalents of DDQ. This information in conjunction with nmr data infers that the desired furan **9a** had been produced. Similarly triarylbutanone **8b** afforded furan **9b** in 26% isolated yield.[7] It is important to note that the lactam functionality of the quinoxaline ring gives rise to another position for the potential introduction of diversity.[8]



Scheme 2: i. ethyl pyruvate, MeOH, r.t.; ii. PhCHO, NaH, DMF ,r.t.; iii. $ArC(O)CH_3$, NaH, DMF, r.t.; iv. DDQ, 1,2-DCE, reflux

In a similar fashion 1,3-dimethylquinoxalin-2-one **11** was prepared (Scheme 3) by the condensation of N-methyl-1,2-phenylenediamine **10** with ethyl pyruvate and was further condensed with benzaldehyde to give the styrylquinoxaline **12**. Michael addition of various arylmethylketones was catalyzed by sodium hydride to afford the desired triarylbutanones **13** in good yield in all but one example.[9] Treatment of triarylbutanones **13a-c** with 2.5 equivalents DDQ indeed resulted in conversion to the furans **14**; [**14a** (26%[10]),**14b** (40%), **14c** (5%)].



Scheme 3: i. ethyl pyruvate, MeOH, r.t.; ii. PhCHO, piperidine, AcOH, toluene, reflux; iii. R-(C_6H_4)C(O)CH_3, NaH, THF, r.t.; iv. DDQ, benzene, reflux.

At this point our assignment of the oxidized products as triarylfurans was confirmed by X-ray analysis of a single crystal of **14a** (Figure 1) which clearly showed the triarylfuran compound with each of the aryl rings rotated out of the plane of the furan ring.[11] The *p*-bromophenyl ring adopts the more coplanar orientation. Relevant torsion angles are: O1-C2-C6-C7, 40.1(7)°; O1-C5-C21-C22, 6.6(10)°; and C2-C3-C15-C16, 39.6(9)°.

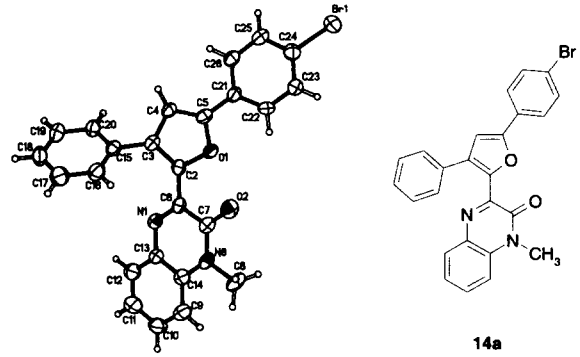


Figure 1: ORTEP representation of furan **14a**. Anisotropic displacement ellipsoids for non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

In summary, a novel, short synthesis of triarylfurans under mild conditions has been developed. An important feature of this synthesis is the ability to install all three aryl rings independently in a step-wise fashion resulting in increased ease of diversity introduction. Application of this methodology towards the parallel synthesis of an array of triarylfurans, the substitution of alternative aromatic and heteroaromatic rings for quinoxaline and investigations into the mechanism of the cyclization reported in this letter are underway and will be reported in due course.

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[1] For a thorough review see *Comp. Heterocylc. Chem.*, Volume 4, Part 3, Katritzky AK and Rees CW. eds., **1984**. Pergamon Press.

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[7] The cyclization reactions described in this letter are generally very clean (TLC analysis), but the yield of isolated products are only moderate (usually in the range of 25-40%). It is not yet established whether this low yield is due to a problem with isolation and/or with unidentified side-reactions.

[8] Treatment of **9** with NaH followed by MeI affords a 9:1 mixture of N/O-methylated products.

[9] 4-Nitroacetophenone failed to give any Michael addition product with **12** under a variety of base-catalyzed conditions (NaH, LDA, *n*-BuLi, solvents, temperatures).

[10] Furan **14a** was prepared as follows: A solution of ketone **13a** (0.25 g; 0.54 mmol.) in benzene (10.0 mL) was treated with DDQ (0.31 g; 2.5 eq.) and the solution was stirred and heated at 95° (oil-bath temp.) for 1h. The mixture was diluted with ethyl acetate, washed with 10% aqu. sodium hydroxide then with water, dried (Na_2SO_4) and evaporated. The residue was purified by flash-chromatography (silica gel, 20% ethyl acetate/hexanes) to afford furan **14a** (0.063 g; 26%) as a yellow solid. mp 186-188°. ^1H NMR (300MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.73-7.71 (m, 2H), 7.61-7.50 (m, 5H), 7.38-7.32 (m, 5H), 6.99 (s, 1H) and 3.72 (s, 3H); Anal. ($C_{25}H_{17}N_2O_2Br$) calcd: C, 65.66; H, 3.75; N, 6.13 found: C, 65.44; H, 3.82; N, 5.93.

[11] *Crystal data and structure solution and refinement for* **14a**. $C_{25}H_{17}BrN_2O_2$, M_r = 457.32, monoclinic, space group $P2_1/c$, a = 19.982(5)Å , b = 8.019(5)Å, c = 13.133(5)Å, β = 101.425(5)°, V = 2063(2)Å^3, Z = 4, F(000) = 928, d_{calc} = 1.473 Mg/m^3, μ = 2.017 mm^{-1}. Data were collected at 223(2) K on an Enraf Nonius CAD-4 diffractometer using graphite monochromated molybdenum radiation (λ = 0.71069Å) and an ω-2θ variable speed scan technique to 2θ ≤ 50°. The 4466 reflections measured were corrected for absorption (ψ-scans; min./max. transmission,0.23/0.83), and averaged to 3638 unique (R_{int}= 0.075) data. The structure was solved by direct methods (Altomare A, et al., SIR-92, University of Bari, Italy, 1992) and refined using full-matrix least-squares on F^2 (Sheldrick GM, SHELXL-93, Program for the Refinement of Crystal Structures, University of Gottingen, Germany, 1993) Positions for non-hydrogen atoms were eventually refined with anisotropic displacement parameters. The hydrogen atoms were included in an idealized position riding on the atom to which they are attached with isotropic displacement factors assigned as a constant (1.2, 1.5 for methyl) times Ueq of the attached atom. The refinement converged (Δ/σ_{max} = 0.00) to values of the conventional crystallographic residuals R = 0.069 for observed data (2527 data; I>2σ(I)) and R = 0.111 (wR2 = 0.236) for all data. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.