Tandem Generation And Trapping of Furo[3,4-*b*]pyrazine/ furo[3,4-*b*]quinoxaline Intermediates By The Coupling Of *o*-Alkynylheteroaryl Carbonyl Derivatives With Fischer Carbene Complexes For Synthesis of Nitrogen Heterocycles

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ABSTRACT

A new route for the tandem generation of furo[3,4-*b*]pyrazine/ furo[3,4-*b*]quinoxaline intermediates by the coupling of *o*-alkynylheteroaryl carbonyl derivatives with Fischer carbene complexes has been described. The intermediates can be trapped through Diels–Alder reaction with dienophiles leading to the synthesis of nitrogen containing heterocyclic analogues of quinoxaline and phenazine, respectively, in one-pot.

*Keywords****:*** Fischer Carbene Complexes, Dotz Benzanullation, Heterocycles, Cycloaddition, Benzannulation.

**1. INTRODUCTION**

Quinoxaline derivatives have received considerable interest from the pharmaceutical industry because of their interesting therapeutic properties such as antiviral, antibacterial, anti-inflammatory, anti-protozoaval and as kinase inhibitors.1 They have also been evaluated as anticancer, anthelmintic agents, antifungal and insecticidal agents.2 In addition, quinoxaline nucleus is a part of several antibiotics such as echinomycin, levomycin, and actinomycin which are known to inhibit the growth of gram-positive bacteria and active against various transplantable tumors.3 Besides this, they have found applications as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents.4,5 Since they display a broad spectrum of biological properties, they are considered as privileged structures in combinatorial drug discovery. Drug formulations containing quinoxalines such as lamprene for leprosy, BMS-238497 for kinase inhibitor, XK-469 as anticancer are currently available (Figure 2.1).



**Figure 2.1**  Biologically active quinoxalines.

Phenazine natural products are isolated as secondary metabolites primarily from *Pseudomonas*, *Streptomyces*, and a few other genera from soil or marine habitats. The biological properties of this class of natural products include antibiotic, antitumor, antimalaria, and antiparasitic activities. The role of phenazine pigments as antibiotics and virulence factors has been briefly reviewed recently.6 Phenazines are redox-active and can reduce molecular oxygen, leading to the generation of toxic reactive oxygen species and explaining their broad-spectrum antibiotic activity. They also act as virulence factors in human infectious disease. For example, pyocyanin induces apoptosis in neutrophils, and strains of *Pseudomonas aeruginosa* defective in pyocyanin synthesis are more susceptible to immune responses in a mouse model of lung infections.7 Since the lungs of nearly all victims of cystic fibrosis are chronically colonized by *P. aeruginosa* and this infection contributes significantly to the low life expectancy of these patients,8 phenazine production may present an attractive target for pharmaceutical intervention.



**Figure 2.2**  Biologically active phenazines.

These heterocyclic ring systems are most commonly assembled by the annulation of a heterocyclic ring onto a pre-existing benzene ring.9 Yadav and co-workers reported the synthesis of quinoxalines from *α*-diazoketones and aryl 1,2-diamines using 10 mol% of copper(II) triflate in excellent yields with high selectivity.9a Rh2(OAc)4 is also found to be an equally effective catalyst for this transformation (Scheme 2.1).



**Scheme 1**

Condensation of 1,2-dicarbonyl compounds and different substituted *o*-phenylenediamines give functionalized quinoxalines at room temperature in DMSO using a catalytic amount of molecular iodine in excellent yields and co-workers (Scheme 2.2).9e



**Scheme 2**

A novel multicomponent reaction involving *o*-phenylenediamines, aldehydes and *p*-tolunesulfonylmethyl isocyanide (TosMIC) in the presence of a base leading to the formation of quinoxalines in very good yields was reported by Tsoleridis and co-workers (Scheme 2.3).9g



**Scheme 3**

In 1901, one of the methods for preparation of phenazines was reported by Wohl and Aue.10 They reported that anilines and nitrobenzenes form phenazines or phenazine-*N-*oxides upon heating to 200 °C in the presence of a strong base (Scheme 4). Drawbacks of this method are that yields were modest and significant amounts of byproducts, primarily consisting of azacompounds, were formed under the harsh reaction conditions (Scheme 2.4).



**Scheme 4**

Synthesis of phenazines by sequential palladium(II)-catalyzed aryl amination using BINAP as ligand was reported by Emoto and co-workers (Scheme 2.5).11a

**Scheme 5**

N-Aryl-2-nitrosoanilines, available from the reaction of nitroarenes with anilide anions, undergo cyclization to furnish substituted phenazines. The reaction is promoted by potassium carbonate in methanol, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in aprotic solvents, and by acetic acid. The method is illustrated by the synthesis of 1-methoxyphenazine, a precursor of pyocyanine, starting from the appropriate nitroarene–aniline pairs (Scheme 2.6).11b



**Scheme 6**

**2. PRESENT WORK**

Multicomponent reactions (MCRs) which could be briefly defined as processes in which at least three reagents, added at the same time and under same conditions, come together in a single reaction vessel to form a new product which contains portions of all of them, have received great attention because of their higher atom economy and their applications in combinatorial chemistry and diversity-oriented synthesis. On the other hand, group VI Fischer carbene complexes (FCCs) which act as valuable reagent in synthetic organic chemistry can be used as important building blocks in MCRs. Several reviews have appeared in this area describing the versatile use of FCCs in MCRs.12

In this Chapter, we have demonstrateda muticomponent coupling approach for the synthesis of quinoxaline and phenazine derivatives by using chromium Fischer carbene complexes. Our strategy toward quinoxaline and phenazine syntheses are based on the pioneering work of Herndon and co-workers.13 The synthetic approach involves a simultaneous one-pot construction of quinoxaline or phenazine rings which occurs in conjunction with the tandem generation and trapping of an azaisobenzofuran intermediate.14 The synthesis involves the coupling of Fischer carbene complexes **2** with 2-alkynyl-3-pyrazine carbonyl derivatives **1A**, followed by the generation of a hitherto unknown intermediate e.g. furo[3,4-*b*]pyrazine **3A** and trapping of the latter with dienophiles. Phenazine derivatives **4** can be synthesized using similar methodology from the coupling of 2-alkynyl-3-quinoxaline carbonyl derivative **1C** through the generation and trapping of furo[3,4-*b*]quinoxaline intermediates **3C** (Scheme 2.7).15



**Scheme 7**

3. **RESULTS AND DISCUSSION**

*3.1.* ***Synthesis of alkynyl-carbonyl derivatives* 1**

Requisite alkynyl-carbonyl derivatives **1A/1C** required for the synthesis of quinoxalines and phenazines were prepared according to the sequence of reactions in Scheme 2.8. Chloroketones **7**/**11** were prepared by the regioselective *ortho-*lithiation of 2–chloropyrazine (**5**)/ 2–chloroquinoxaline (**9**) with LiTMP at –78 °C followed by quenching with benzaldehyde and subsequent oxidation according to the procedure Turck and co-workers.16 Iodoketone **8** was prepared in 80% yield from (3-chloro-2-pyrazinyl)phenylmethanone17 by halogen exchange with NaI in acetonitrile. Iodoketone **8** or chloroketone **11** were reacted with (trimethylsilyl)acetylene under palladium catalysis in the presence of a catalytic amount CuI to give requisite *o*-alkynylcarbonyl derivatives **1A** or **1C** respectively.

The synthesis of 2-alkynyl 3-formylquinoxaline derivative **1B** commenced with coupling of commercially available *o*-pheylenediamine **12** and pyruvic acid. The coupled product **13**, thereafter was reacted with POCl3 in reflux condition to give the chloro derivative **14**. Subsequent oxidation with selenium dioxide where 1,4-dioxane was used as solvent, delivered the 2-chloro-3-quinoxaline carboxaldehyde **15**.18 Sonogashira coupling of **15** with (trimethylsilyl)acetylene at room temperature under palladium catalysis in the presence of a catalytic amount CuI afforded the requisite alkynyl carbonyl derivatives **1B**.



**Scheme 8**



**Scheme 9**

*3.2.* ***Preparation of carbene complexes***

Pentacarbonyl(methoxymethylcarbene)chromium (**2)**19 was prepared from the methyllithium and chromium hexacarbonyl at 0 °C under argon atmosphere, followed by the conversion to the ammonium salt **16**20 with the addition of tetraethylammonium bromide and then treatment with methyl iodide in presence tetrabutylammonium bromide (Scheme 2.10).21



**Scheme 10**

The *γ,δ*-unsaturated Fischer carbene complex **17** was prepared from the methoxymethylcarbene complex **2** in 66% yield *via* deprotonation using *n*-BuLi (0.95 eq) at –78 °C followed by addition of an excess allylic bromide at once at 0 °C as reported by Herndon and co-workers (Scheme 2.11).22,23



**Scheme 11**

*3.3.* ***Three-component coupling reaction of carbene complex, alkynyl carbonyl derivatives and dienophiles***

*3.3.1.* ***Synthesis of quinoxaline derivatives***

The three component coupling reaction of pyrazinyl ketone **1A**,carbene complex **2** and *N*-phenylmaleimide (~ 1:1:1 ratio) inrefluxing THF was initially investigated (Scheme 2.12). This reaction led to a mixture of oxanorbornene derivative **20** and quinoxaline derivative **21** through the tandem generation and trapping of the furo[3,4-*b*]pyrazine intermediate **3A**.

In this reaction, coupling of the carbene complex **2** with the alkyne **1A** initially provides intermediate alkyne carbene complex **18**, which is then captured by the oxygen to form the carbonyl ylide derivative **19**. Loss of metal from the carbonyl ylide leads to the isobenzofuran derivative **3A**, which then undergoes Diels-Alder reaction with *N*-phenylmaleimideafforded the mixture of oxa-bridged adduct **20** (42% yield) and the quinoxaline derivative **21** (30%) yield. The formation of the oxa-bridged adduct **20** was evident from spectral data. Presence of absorption band at 1713 cm-1 due to carbonyl group in the IR spectra; in the 1H NMR spectrum, the two



**Scheme 12**

pyrazinyl protons can be easily assigned since the protons are largely deshielded and they appears at *δ* 8.37 (d, 1H, *J*=2.8 Hz) and 8.33 (d, 1H, *J*=2.8 Hz). Other characteristic signals are at 3.68 and 3.59 (d, *J* = 18.0 Hz, *AB* system) for C*H*2COMe, 3.95 and 3.56 (d, 1H, *J* = 6.8 Hz) for two C*H*CON and 2.40 (s, 3H) for CH2COC*H3*; peaks at *δ* 202.9 (*C*OCH3), 172.9 & 171.2 (two *C*ONPh), 89.4 & 85.3 (bridged *C*O*C*), 52.4 and 50.3 (two *C*HCON) along with other 14 lines in the 13C NMR spectrum and the molecular ion peak at *m/z* 426 ([MH]+, C25H19N3O4) in the mass spectrum revealed the formation of compound **20**. The stereochemistry of the oxa-bridged adduct **20** is *exo* which can be anticipated from the chemical shifts of HA and HB (< 4 ppm).25 The structure of **21** was also assigned from the spectral data. Presence of absorption band at 1714 cm-1 due to carbonyl group in the IR spectra; in the 1H NMR spectrum, the two pyrazinyl protons can be easily assigned since the protons are largely deshielded and they appears at *δ* 8.99 (d, 1H, *J*=1.5 Hz) and 8.97 (d, 1H, *J*=1.5 Hz). 5.08 (s, 2H, C*H*2COCH3) and 2.50 (s, 3H, CH2COC*H*3) and disappearance of signals at 3.68 and 3.59 (d, 1H, C*H*2COMe), 3.95 and 3.56 (d, 1H, C*H*CON) corresponding to the oxa-bridged adduct **20** and the molecular ion peak at *m/z* 408 ([MH]+, C25H20N3O4) in the mass spectrum thus indicating that this is a fully aromatized compound. In the 13C NMR appearance of 21 lines and the disappearance of signals at *δ* 52.4 & 50.3 (two CH*C*ON) and 89.4 & 85.3 (bridged *C*O*C*) accounts for the structure of compound **21**.

Similar type of coupling was also tested using *N*-methylmaleimide as dienophile. In this reaction the *in situ* generated *α*-methylsubstituted furo[3,4-*c*]pyrazine intermediate underwent a [4+2] cycloaddition reaction with the dienophile afforded quinoxaline derivative **222** as the sole product(Scheme 2.13). In this reaction, initially formed Diels–Alder oxa-briged adduct **26** were not stable under reaction conditions and readily converted to the quinoxaline derivatives **22**.



**Scheme 13**

The reaction was also examined with dimethyl maleate as the dienophile (Scheme 2.14). The reaction of pyrazinyl ketone **1A**, carbene complex **2** and dimethyl maleate under the same conditions as previously described afforded the three component coupling product **24** in 40% yield via the unstable enol ether **23**. No aromatized product was isolated, even under mild acidic condition. The structure of quinxaoline derivative **24** was evident from spectral data. The presence of molecular ion peak at *m/z* 379 ([MH]+, C21H20N2O6) in the mass spectrum. In the 1H NMR spectrum, the two pyrazinyl protons can be easily assigned since the protons are largely deshielded and they appear at *δ* 8.33 (bs, 2H). Other characteristic signals are at 3.71 and 3.33 (d, *J* = 17.4 Hz, *AB* system) for C*H*2COMe, 3.95 and 3.46 (d, 1H, *J* = 4.8 Hz) for two C*H*CON, 3.78 and 3.51 (s, 3H) for two CO2C*H*3 2.27 (s, 3H) for CH2COC*H3*; peaks at *δ* 203.0 (*C*OCH3), 171.2 and 169.9 (two *C*O2Me), 88.2 and 85.3 (bridged *C*O*C*), 30.9 (CH2CO*C*H3) along with other 13 lines in the 13C NMR spectrum and the molecular ion peak at *m/z* 379 ([MH]+, C21H20N2O6) in the mass spectrum revealed the formation of compound **24**.



**Scheme 14**

*3.3.2.* ***Synthesis of phenazine derivatives***

The three component coupling reaction of *o*-alkynyl quinoxaline carbonyl derivative **1B**, carbene complex **2** and *N*-phenylmaleimide was also examined. In this case, tandem generation and trapping of the desired furo[3,4-*b*]quinoxaline intermediate **3B** proceeded smoothly to give the corresponding hetero-polyaromatic phenazine derivatives **27** (Scheme 2.15). Although the [4+2] oxa-bridged adduct **25** was isolated, but it readily converts to **27** in chloroform at room temperature.



**Scheme 15**

The presence of signals at *δ* 5.87 (s, 1H, C*H*OC), 3.62 and 3.55 (*AB* pattern) and doublets at 3.76 and 3.46 (C*H*CON) in the 1H NMR confirmed the formation of the oxa-bridged adduct **25.** The stereochemistry of the oxa-bridged adduct **25** was assigned as *exo* based on the *zero* Hz coupling of HA and HB the chemical shifts of Hb and Hc (< 4 ppm).25 The gross structure of phenazine derivative **27** is settled on the basis of the spectral data. In the IR spectrum, the presence of absorption bands at 1713 cm-1 confirms the presence of keto group. The 1H NMR spectrum of **27** shows characteristic signals at *δ* 8.77 (s, 1H, aromatic proton), 5.15 (s, 2H, C*H*2OCH3), 2.53(s, CH2COC*H3*) with the disappearance of signals at 5.87 (s, 1H, C*H*OC), 3.62 and 3.55 (*AB* patterns) and doublets at 3.76 and 3.46 (C*H*CON) in **25**. Similar type of coupling was also tested using *N*-methylmaleimide as dienophile. In this reaction the *in situ* generated *α*-methylsubstituted furo[3,4-*c*]quinoxaline intermediate **3B** underwent a [4+2] cycloaddition reaction with the dienophile afforded quinoxaline derivatives **28** as the sole product. In this reaction, initially formed Diels–Alder adducts **26** were not stable under reaction conditions and readily converted to the quinoxaline derivatives **28**. The structure of the phenazine derivative **28** was established with the help of spectral data as previously described.

*3.3.3.* ***Synthesis of heterocyclic analogues of 1-arylnaphthalene lignans***

Heterocyclic analogues of 1-arylnaphthalene lignans are synthetic analogues of lignan in which the naphthalene ring has been replaced by a heteroaromatc ring, and or pendant aromatic ring by heteroaromatic ring. These compounds have attracted the attention of both synthetic and medicinal chemists because many of them exhibit interesting biological activities. In our studies, the initially formed oxa-bridged cycloadduct **20** from the three-component coupling of alkynyl carbonyl derivative **1A**, carbene complex **2** and the dienophile, could be readily cleaved leading to the substituted quinoxaline **21** using DBU in refluxing toluene (Scheme 2.16).26 The quinoxaline derivatives **21** and **22** may be viewed as heterocyclic analogue of 1-arylnaphthalene lignans.



**Scheme 16**

*3.4.* ***Coupling of o-alkynyl pyrazine/quinoxaline carbonyl derivatives with γ,δ-unsaturated Fischer carbene complex: Synthesis of azahydrophenanthrone derivatives***

As part of a general effort to prepare aza-analogues of hydrophenanthrene natural products (including morphine alkaloids and abietanes) and tetracyclic triterpenes, the coupling of *o-*alkynyl pyrazine/quinoxaline carbonyl derivatives **1A**/**1C** with simple *γ,δ*-unsaturated Fischer carbene complex **17** was investigated. This reaction proceeds *via* a tandem process involving the formation of azaisobenzofuran **29**, followed by *exo* selective intramolecular Diels–Alder reaction, and ring opening of **30** to afford azahydrophenanthrone derivatives **31**/**32** exclusively, in satisfactory yield (Scheme 2.17). The *exo* Diels-Alder adduct has been depicted and is anticipated on basis of six-membered ring-forming intramolecular Diels-Alder reactions of isobenzofurans are normally *exo* selective as from literature precedent.27 The initial Diels-Alder adduct **30**, resulting from **29**, appears to be unstable with respect to ring opening processes. The crude reaction mixture also showed an impurity consistent with enol ether **30** (benzo analogue), which hydrolyzed to **32** during chromatographic purification. This was confirmed by the presence of peak at 3.71ppm due to OC*H3* in the 1H NMR spectrum of the crude product.



**Scheme 16**

The structural assignment for **31/32** is based on the interpretation of IR, 1H-, 13C-NMR spectra as well as elemental analysis. For compound **31**, IR spectrum displayed absorption at 3417 and 1649 cm-1 representing a hydroxyl group and an *α*, *β*-unsaturated ketone functionality in the system; in the 1H NMR spectrum, the two pyrazinyl protons can be easily assigned since the protons are largely deshielded and they appears at *δ* 8.61 (d, 1H, *J*=2.2 Hz) and 8.58 (d, 1H, *J*=2.2 Hz). The aliphatic region is rather crowded and the signals at *δ* 4.15 (s, 1H, exchangeable with D2O, O*H*), 2.43 (dd, 1H, *J*=12.8, 3.7 Hz), 1.93 (m, 1H), 1.82 (m, 1H), 0.20(s, 9H) which are indicative of the formation of compound **31**. Additionally, in the 13C NMR presence of carbon signals at *δ* 203.7 (*C*O), 75.4 (*C*(OH)PH), 2.9 (3C, Si*C*H3) and the presence of molecular ion peak at *m*/*z* 365 ([MH]+, C21H24N2O2Si) in MS and anal. calcd for C21H24N2O2Si: C, 69.19; H, 6.64; N, 7.69. Found: C, 69.01; H, 6.86; N, 7.76.

4. **CONCLUSION**

We have demonstrated a new route for the tandem generation of furo[3,4-*b*]pyrazine/ furo[3,4-*b*]quinoxaline intermediates by the coupling of *o*-alkynylheteroaryl carbonyl derivatives with Fischer carbene complexes. The intermediates can be trapped through Diels–Alder reaction with dienophiles leading to the synthesis of nitrogen containing heterocyclic analogues of quinoxaline and phenazine, respectively, in one-pot. This is the first report of in situ generation of furo[3,4-b]pyrazine intermediates.

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