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Methodology towards aryl-1, 2-azoles: An overview

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ABSTRACT

Aryl-1, 2-azoles are important class of compounds in organic chemistry. These aryl-1, 2-azoles and its analogues have tremendous importance in synthetic and medicinal chemistry. Therefore, a large number of studies on their synthesis have been reported in the literature. The aryl-1, 2-azoles or their simpler analogues have potential as drugs for antiviral, antimicrobial and antitumor activities. This microreview will discuss some of the recent synthetic studies towards the synthesis of aryl-1, 2-azoles and their analogues. © 2008 Trade Science Inc. -INDIA

KEYWORDS

Aryl-1, 2-azoles;
pyrazoles;
1, 3-diketones;
Suzuki coupling;
Stille coupling;
α-aroylacetones;
Weinreb amides.

INTRODUCTION

Aryl-1, 2-azoles are important class of compounds in synthetic organic chemistry and they possess various biological activities; therefore, a large number of studies on their synthesis have been reported so far. New routes to pyrazoles, isoxazoles continue to be of interest to the synthetic community, as these moieties are common in pharmacologically active compounds and natural products[1]. In contrast, till date the synthesis of aryl-1, 2-azole compounds has been somewhat limited by the available synthetic methodology. Moreover, the reported synthetic approaches towards the synthesis of aryl-1, 2-azoles are based on condensation of 1, 3-diketones with hydrazine and hydrazine derivatives[2]. Other methods for the synthesis of pyrazoles that do not require the 1, 3-diketones have also been reported[3] but tend to have their own drawbacks like step-intensive. In light of this, it is clear that using 1, 3-diketones as an intermediate is the broadest and most efficient route to azoles[4].

Pyrazoles **(1a/1b)** and isoxazole **(1c)** (Figure 1) are an important class of hetero-aromatic ring systems that find extensive use in the pharmaceutical industry. The aryl-1, 2-azoles **(2 and 3)** are the part of the general azoles family with an aromatic ring directly attached either at the 3rd or 5th position of **(1)**. Although a signifi-

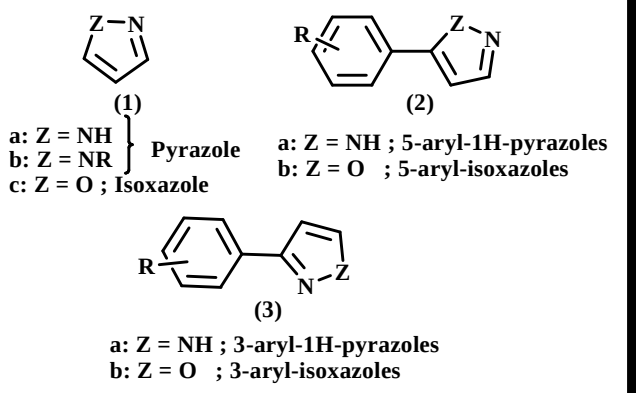


Figure 1: General structure for aryl-1, 2-azoles

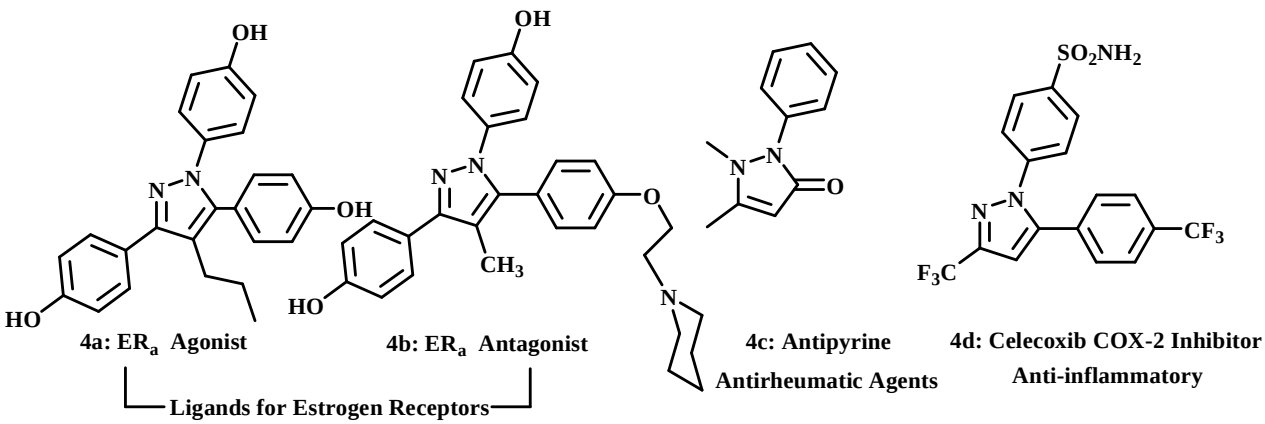


Figure 2: Representative examples of biologically active compounds containing aryl-1,2-azole moiety

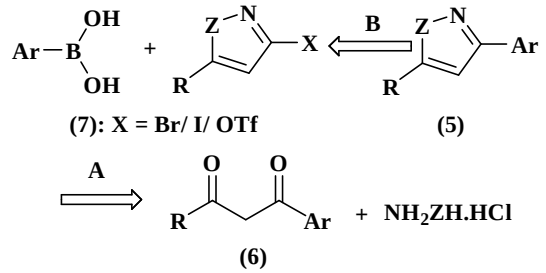
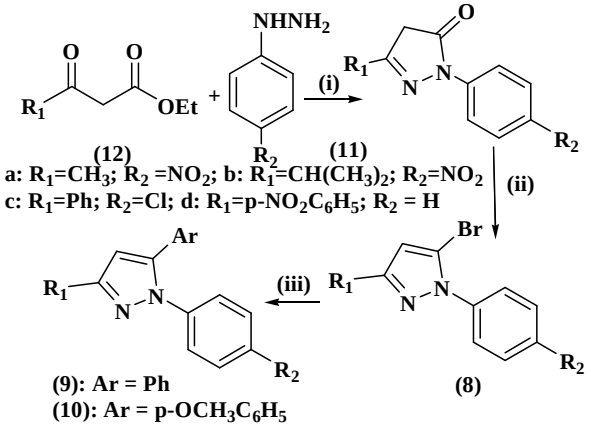


Figure 3: Reterosynthetic approach for aryl-1,2-azoles



a: R$_1$=CH$_3$; R$_2$ =NO$_2$; b: R$_1$=CH(CH$_3$)$_2$; R$_2$=NO$_2$
c: R$_1$=Ph; R$_2$=Cl; d: R$_1$=p-NO$_2$C$_6$H$_5$; R$_2$ = H

SCHEME 1: (i) AcOH, reflux, 4h; (ii) PBr$_3$, CH$_3$CN, reflux; (iii) ArB(OH)$_2$, 2% Pd(Ph$_3$)$_4$, 2M Na$_2$CO$_3$ THF, reflux, 4h

cant number of biologically important aryl-1, 2-azoles are scattered in the literature, a few representative examples containing the aryl-1, 2-azole motif **(4a-4d)** are given in figure 2.

Incorporation of aryl unit to the azoles **(5)** is another major interesting task in synthetic organic chemistry. The various reported synthetic approaches are based on condensation of 1, 3-diketones with hydrazine and hydrazine derivatives (route A, Figure 3) or transition-metal catalyzed arylation on fully assembled azoles (route B, Figure 3)[5,6]. The success of route A is completely dependent on the availability of pure of 1, 3-diketones **(6)** as well as on the regioselectivity during the condensation. Similarly, the success of route B is dependent on the availability of the corresponding halides or triflates **(7)** of the corresponding azoles and the selectivity of N- verses C-arylation under the particular reaction condition.

The objective of this review presented herein is to provide a brief summary of the recent methods available for the synthesis of aryl-1, 2-azoles and their analogues. The literature in this review is covered until December 2007.

Different synthetic strategies for aryl-1, 2-azoles

Methods available for the formation of aryl-1, 2-azoles fall into one of the following categories.

1. Transition-metal catalyzed arylation on fully assembled azoles

Wang et al. performed Suzuki coupling on 1-aryl-5-bromopyrazoles **(8)**[7]. The cross-coupling of 1-aryl-5-bromopyrazoles **(8)** with aryl boronic acids promoted by Pd(PPh$_3$)$_4$ afforded unsymmetrical 3, 5-disubstituted 1-arylpyrazoles **(9)** and **(10)** in excellent yields. 1-Aryl-5-bromopyrazoles **(8)** were prepared from their corresponding 1-arylpyrazolones **(11)** with PBr$_3$ in refluxing acetonitrile (SCHEME 1).

Zhang and co-workers utilized the Suzuki coupling

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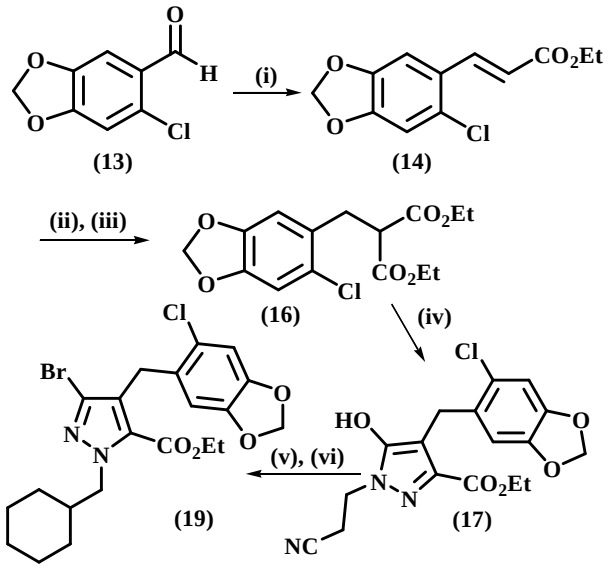
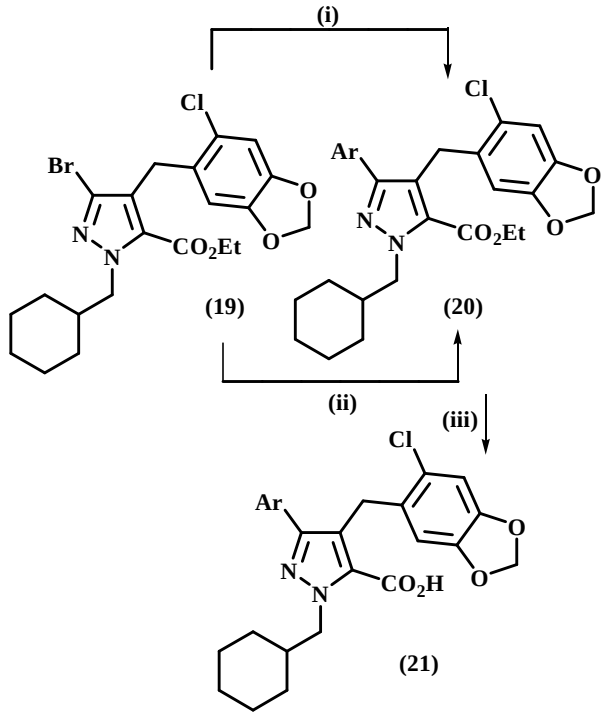
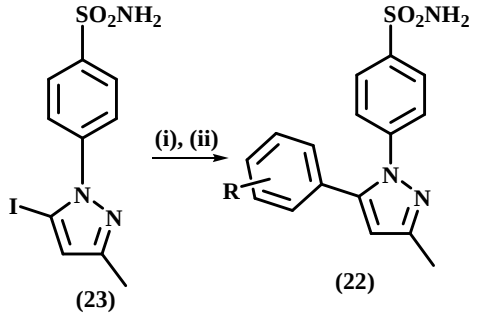


SCHEME 2: (i) $EtO_2CCH_2PO(OEt)_2$, NaH/DME, rt, 2.5h, 90%; (ii) $NaBH_4$, $CuCl_2$, THF/EtOH; (iii) EtO_2CCO_2Et NaOEt, toluene, reflux, 3h, 76%; (iv) $NCCH_2CH_2NHNH_2$, AcOH, 100°C, 1h; (v) $POBr_3$; (vi) NaH, DMF, cyclohexylmethyl bromide, rt-60°C, 16h, 55%.



SCHEME 3: (i) $ArSnBu_3$, $Pd(PPh_3)_4$, toluene, 5h; (ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, DMF, 24h; (iii) 2N NaOH, reflux, 2h

of a 5-bromopyrole while exploring the structure-activity relationship of endothelin antagonists[8]. Pyrazole-5-carboxylic acids **(12)** were obtained by the route



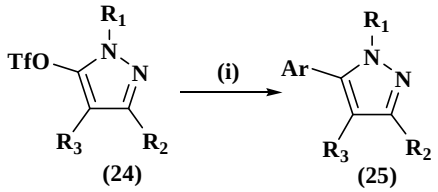
SCHEME 4: (i) Pd/C (5%), $ArB(OH)_2$, Na_2CO_3, (ii) $MgSO_4$

outlined in SCHEMES 2 and 3. Wittig-Horner reaction of 6-chloropiperonal **(13)** with triethyl phosphono acetate in DME in the presence of NaH afforded unsaturated ester **(14)**. After reduction of the double bond with $NaBH_4/Cu_2Cl_2$ in a mixture of THF/EtOH, the saturated ester derivative **(18)** was obtained in modest yield. Reaction of **(15)** with diethyl oxalate in toluene in the presence of NaOEt gave **(16)**, which was cyclized to form the hydroxypyrazole **(17)** by the reaction with cyanoethylhydrazine in AcOH. Bromopyrazole **(18)** was obtained after OH-bromine exchange in pure $POBr_3$ at 60°C. The deprotection of the bromopyrazole **(18)** was realized by a retro-Michael-type reaction on the cyanoethyl substituent by treatment with NaH in DMF. The ionic pyrazole intermediate was regio-selectively alkylated in situ with cyclohexylmethyl bromide, which afforded the desired compound**(19)**(SCHEME 2).

Suzuki reaction or Stille coupling of **(19)** with the requisite aryl boronic acids or aryl stannanes gave the corresponding pyrazoles **(20)**, which after saponification under standard reaction conditions yielded the desired pyrazole-5-carboxylic acids **(21)** (SCHEME 3).

Organ et al. prepared a library of COX-2 inhibitors **(22)** from 4-(5-iodo-3-methyl pyrazolyl) phenylsulfonamide **(23)** and aryl boronic acid by solution phase Suzuki coupling utilizing a solid-supported catalyst (SCHEME 4)[9].

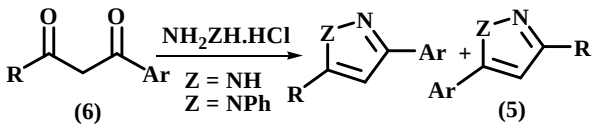
Dvorak et al. have developed a general protocol for the palladium-mediated Suzuki coupling reaction of pyrazole triflates **(24)** and aryl boronic acids (SCHEME 5)[10]. This is a mild and efficient method for incorporating an aryl ring onto a pyrazole scaffold. The coupling conditions were found to be tolerant of a broad range of electronic and steric variations in either the boronic acid or pyrazole triflate components.



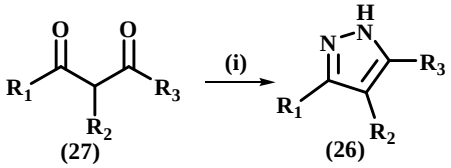
a: $R_1 = R_3 = H$; R_2: CH_3
b: $R_1 = CH_3$; $R_3 = H$; R_2: CF_3
c: $R_1 = Ph$; $R_3 = H$; R_2: CF_3
d: R_1 =Ph; $R_3 = H$; R_2: CH_3
e: R_1 =CH_3; $R_3 = H$; R_2: CF_3
f: R_1 =CH_3; $R_3 = H$; R_2: CH_3

a: Ar = Ph
b: Ar = 4-OCH_3Ph
c: Ar = 2-CH_3Ph

SCHEME 5: (i) $ArB(OH)_2$, K_3PO_4, 8% $PdCl_2$(dppf)/4% dppf, 1,4-dioxane, 100°C

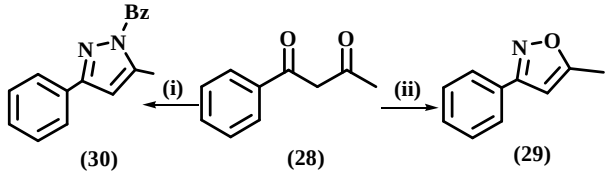


SCHEME 6



a: R_1=Ph, R_2=H, R_3=CH_3; b: R_1=CH_3, R_2=H, R_3=CH_3
c: R_1=Ph, R_2=H, R_3 = Ph; d: R_1 = Ph, R_2=CH_3, R_3=CH_3

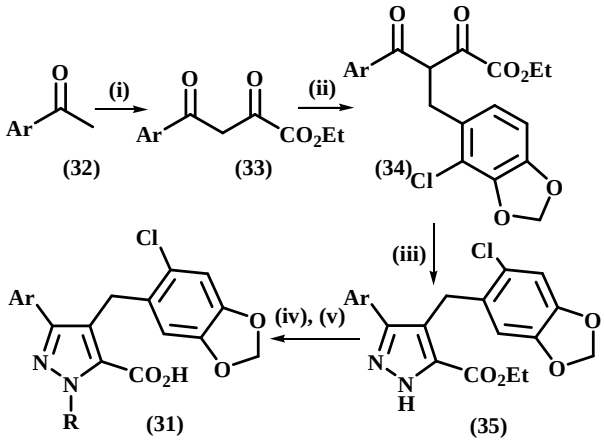
SCHEME 7: (i) $NH_2NH_2.H_2O$, THF



SCHEME 8: (i) $BzNHNH_2$.HCl, (ii) NH_2OH.HCl

2. Condensation of arylated 1, 3-diketones with hydrazine and hydrazine derivatives

The most prevalent method of obtaining azoles is by the reaction of the 1, 3-diketones with hydrazine or hydrazine derivatives. For the synthesis of aryl-azoles **(5)**, the 1, 3-diketones should be α-aroylacetones **(6)** and its derivatives. However, if a diversity-oriented synthesis of pyrazole is desired, this method becomes cumbersome as each 1, 3-diketone must be purified and the product is often obtained as a mixture of condensation products. Furthermore, most electrophilic functional groups such as aldehydes, nitriles, esters, and alkyl halides do not survive in this transformations. Hence it is clear that using 1, 3-diketones as an intermediate is the broadest and most efficient route to azoles.



SCHEME 9: (i) EtO_2CCO_2Et, NaOEt, EtOH, 0°C-rt, 20h; (ii) 6-chloropiperonyl chloride, NaOEt, DMF, NaI, rt, 16h; (iii) $NH_2NH_2OH.H_2O$, EtOH, reflux, 4h; (iv) R-X, NaH, DMF, rt, 20h; (v) 2N NaOH, reflux, 2h

Wiles et al. demonstrated the successful synthesis of an array of 1, 2-azoles **(26)** in a borosilicate glass micro reactor[11]. The treatment of 1,3-diketone **(27)** with 1.1 equivalents of hydrazine monohydrate in THF afforded the respective 1,2-azoles in excellent yields. Large scale synthesis was accomplished using this technique. Using the same reaction conditions, the reaction was repeated in DMF, whereby 100% conversion to the pyrazole **(26a)** was obtained (SCHEME 7).

Having successfully demonstrated the preparation of an array of pyrazoles, the technique was extended to the synthesis of an isoxazole **(29)** and a substituted pyrazole **(30)** from **(28)** (SCHEME 8).

Zhang and co-workers utilized this condensation reaction of 1, 3-dicarbonyl compounds with hydrazine and successfully developed a synthesis of pyrazole-5-carboxylic acids **(31)**[12]. Commercially available ketones **(32)** were treated with diethyl oxalate in the presence of NaOEt in ethanol to give quantitatively the corresponding α,γ-diketoesters **(33)**. Reactions of α, γ-diketoesters **(33)** with 6-chloro-piperonyl chloride were performed in the presence of EtONa and NaI in DMF. The crude compounds **(34)** were allowed to react directly with hydrazine monohydrate in ethanol to afford the desired pyrazole esters **(35)**. Regioselective alkylation of **(35)** with the requisite alkyl halide or alkyl tosylate

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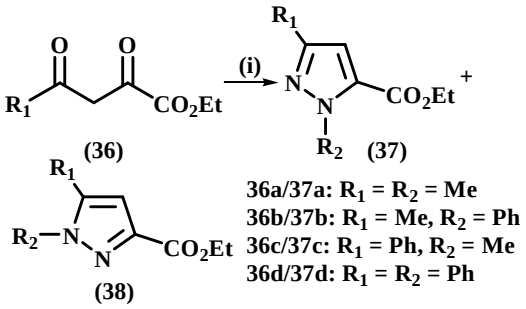
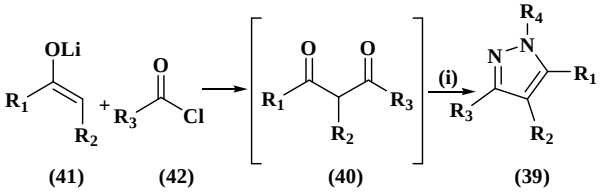
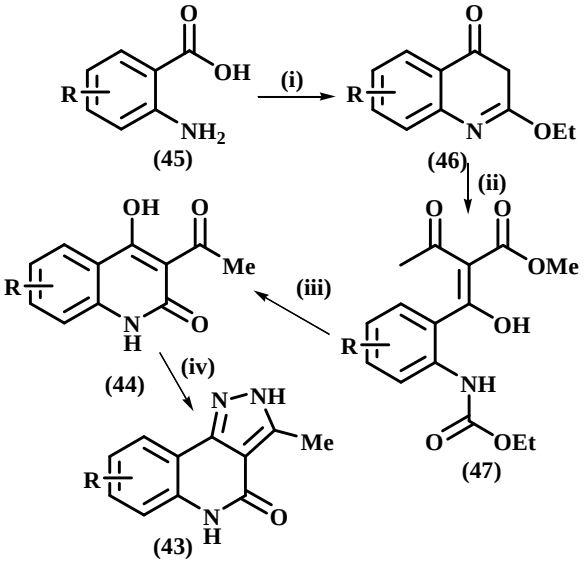


SCHEME 10: (i) $N(R_2)HNH_2$, EtOH, reflux, 3h



SCHEME 11: (i) R_4NHNH_2



SCHEME 12: (i) Ethyl chloroacetate, pyridine, -10°C, 93%; (ii) NaH, ethyl acetoacetate, benzene, 23°C, 85%; (iii) MeOH, NaH, benzene 72°C; (iv) NH_2NH_2, HCl, DMA, 140°C, 81%.

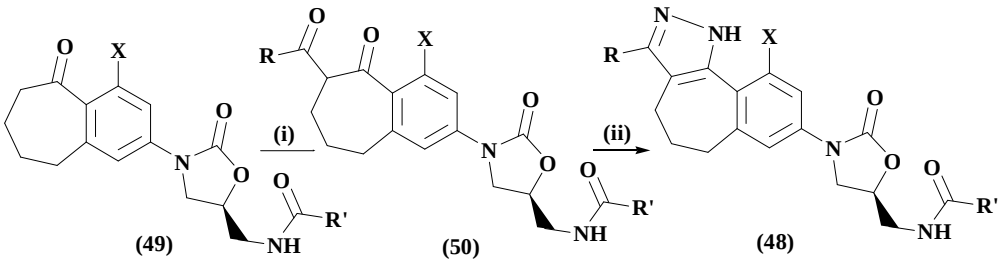
in the presence of NaH in DMF at room temperature followed by saponification gave the pyrazole carboxylic acid **(31)** in good yields (SCHEME 9).

Schmidt and co-workers reported a convenient approach to the synthesis of substituted pyrazole esters by the condensation of β-diketo compounds **(36)** with methyl and phenyl hydrazine[13]. The reaction yielded a 2:1 to 1:2 mixtures of the two isomeric disubstituted pyrazole carboxylic acid ethyl esters **(37)** and **(38)**, respectively. These products were readily separable by column chromatography on silica gel (SCHEME 10).

Heller and co-workers reported a convenient approach to the synthesis of pyrazoles **(39)** by addition of hydrazine with in situ generation of 1, 3-diketones **(40)** from lithium enolate of ketones **(41)** and acid chlorides **(42)** (SCHEME 11)[14]. Most functional groups were tolerated with little or no side product formation, including nitriles, esters, alkyl halides, and electrophiles with enolizable α-protons. This method proved useful for the preparation of fused bicyclic pyrazole systems as well.

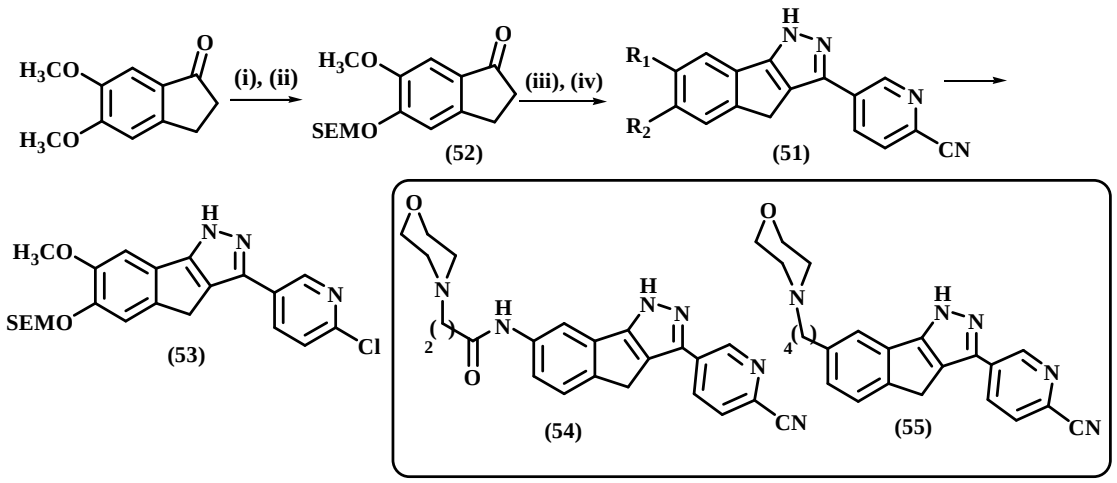
To explore the convenient approach for the synthesis of pyrazoloquinolinones **(43)** by condensation of 4-hydroxyquinolinones **(44)** with hydrazine (SCHEME 12)[15], the substituted anthranilic acids **(45)** were cyclized with ethylchloroacetate to provide benzoxazinones **(46)**. These electrophiles reacted with the sodium anion of ethyl acetoacetate to provide acrylates **(47)** which were cyclized and decarboxylated upon treatment with sodium methoxide to provide 4-hydroxyquinolinones **(44)**.

Boyer et al. have recently reported a series of novel substituted pyrazoles **(48)** which containing conformationally-restricted oxazolidinones possessing Gram-positive and fastidious Gram-negative antibacterial activity[16]. The substituted pyrazoles **(48)** were synthesised

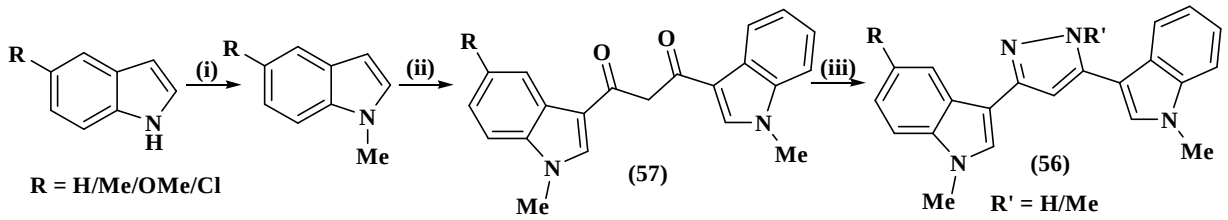


R = H, alkyl, aryl or heteroaryl, R' = alkyl, ary or heteroaryl, X= H, F

SCHEME 13: (i) RCOCl or RCO_2Et, LiHMDs or LDA or t-BuOLi; (ii) hydrazine hydrate, EtOH, rt



SCHEME 14: (i) NaCN, DMSO, 145°C, 53%; (ii) SEMCl, DIEA, CH_2Cl_2, 72%; (iii) NaH, phenyl 6-chloronicotinate, THF; (iv) AcOH, hydrazine, EtOH, 90°C, 81%



SCHEME 15: (i) t-BuOK, MeI, TDA-1/benzene, rt, 24h; (ii) malonyldichloride/DCM, rt, 2h; (iii) $NH_2NH_2.H_2O$ or NH_2NHMe, THF/AcOH, reflux, 24h

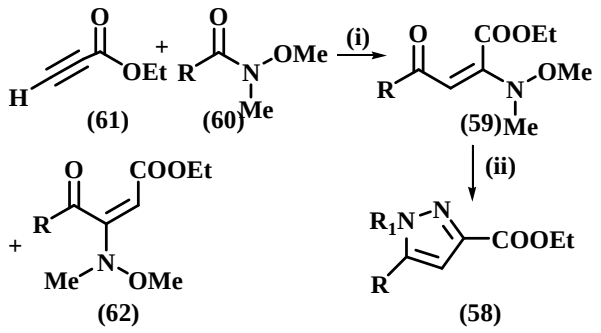
from the ketones **(49)**. Treatment of ketone **(49)** with the appropriate acid chloride or ester in the presence of lithium hexamethyldisilazane or lithium diisopro pylamide or lithium t-butoxide gave the diketo compounds **(50)** which further underwent condensation with hydrazine hydrate gave the desired substituted prrazoles **(48)** (SCHEME 13).

Using this elegant methodology Yunsong Tong *et al*. synthesised a series of 1, 4-dihydroindeno[1,2-c]pyrazole compounds **(51)** with a cyclopyridine moiety at the 3-position of the tricyclic pyrazole core was explored as a potent CHK-1 inhibitors[17]. The chemistry leading to compounds with side chains at the 6- and/or 7-position of the tricyclic pyrazole core via an ether linker (SCHEME 14). The one pot acylation of compound **(52)** by phenyl-6-chloronicotinate using NaH followed by hydrazine and acetic acid to provide **(53)** which is the key step for this route. The synthesis of compounds **(54)** and **(55)** carrying a side chain with an amino or acetylamino linker at the 7-position also achieved by this route.

A series of bis-indolylpyrazoles **(56)** were obtained by cyclization of diketones **(57)** using hydrazine monohydrate or methylhydrazine in refluxing acetic acid/THF[18]. This class of compounds has been stimulated by both their unique chemical structure and the wide range of biological properties including antiviral, antimicrobial and antitumor activities. The 1, 3-bis-indolyldiketones **(57)** appeared as a valuable and versatile intermediate for the synthesis of bis(indolyl)pyrazoles **(56)** (SCHEME 15).

3. Miscellaneous methods for the synthesis of aryl -1, 2-azoles

Recently, Persson and co-workers reported new synthetic precursors for the regioselective synthesis of pyrazoles **(58)** using N-methoxy-N-methyl-β-enaminoketoesters **(59)**[19]. Weinreb amides **(60)** react with the lithium or sodium acetylide of ethyl propionate **(61)** in a acyl substitution-conjugate addition sequence to furnish (E)-N-methoxy-N-methyl-β-enaminoke toesters **(59)**. This approach provides a diverse entry



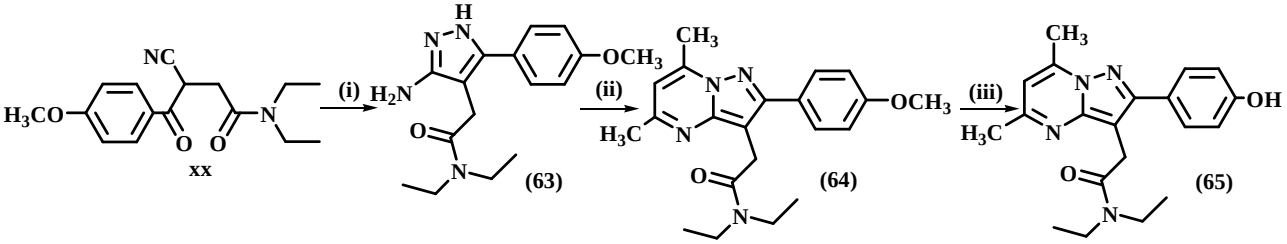
R = Me, Et, Bn, $Ph(CH_2)_2$, i-Pr, t-Bu, Ph, p-$NO_2C_6H_4$, p-$CH_3OC_6H_4$, 2,4-$Cl_2C_6H_3$

SCHEME 16: (i) NaHMDS, THF, -78°C; (ii) R_1NHNH_2, $CDCl_3$, Microwave irradiation

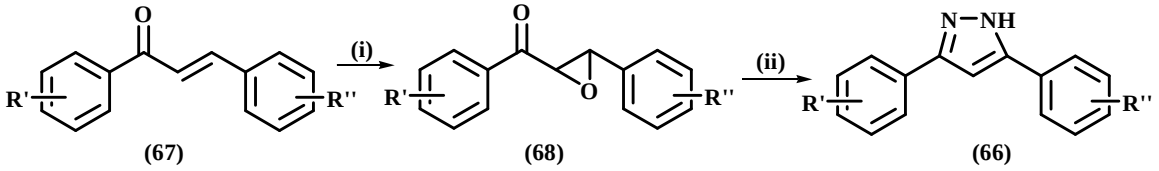
termediate, undergoing microwave-assisted regioselective cyclocondensations in $CDCl_3$, yielding pyrazoles **(58)** in moderate to good yields (SCHEME 16).

The novel pyrazolopyrimidine ligand, N, N-diethyl-2-[2-(4-methoxyphenyl-pyrazolo[1,5-a]pyrimidin-3-yl]-acetamide **(63)** has been reported as potent ligand for the peripheral benzodiazepine receptor displaying an affinity of Ki=4.7nM. Compound **(64)** was subsequently demethylated by heating in 45% HBr to form the phenolic derivative **(65)**(SCHEME 17)[20].

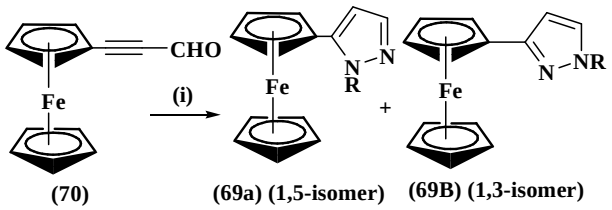
During our design of novel derivatives of chalcones, as analogues of the combretastatins with tubulin bind-



SCHEME 17: (i) hydrazine hydrate, EtOH, acetic acid reflux, 4h; (ii) 2,4-pentadione, EtOH, reflux, 12h; (iii) 48% HBr, 100°C, 7h



SCHEME 18: (i) K_2CO_3, MeOH, rt, H_2O_2; (ii)Hydrazine hydrate, p-toluenesulfonic acid, xylenes, reflux



SCHEME 19: (i) $RNHNH_2$.xHCl

to densely functionalized heterocyclic compounds, including pyrazoles through regioselective cyclocondensations with hydrazines in a microwave-assisted reaction. In all the cases, the total enaminoketoester yield exceeded 60%. Weinreb amides with less substituted α-carbons (R=Me, Et, Bn, $Ph(CH_2)_2$, i-Pr) displayed low selectivity and resulted in the formation of α-enaminoketoesters **(62)** in addition to β-enaminoketo esters **(59)**. Enaminones **(59)** served as a synthetic intermediate, undergoing microwave-assisted regioselective cyclocondensations in $CDCl_3$, yielding pyrazoles **(58)** in moderate to good yields (SCHEME 16).

The novel pyrazolopyrimidine ligand, N, N-diethyl-2-[2-(4-methoxyphenyl-pyrazolo[1,5-a]pyrimidin-3-yl]-acetamide **(63)** has been reported as potent ligand for the peripheral benzodiazepine receptor displaying an affinity of Ki=4.7nM. Compound **(64)** was subsequently demethylated by heating in 45% HBr to form the phenolic derivative **(65)**(SCHEME 17)[20].

During our design of novel derivatives of chalcones, as analogues of the combretastatins with tubulin binding and antitumor properties; heterocyclic derivatives of chalcones were synthesised and studied to establish the cytoxicity[21]. Substituted 3, 5-diarylpyrazoles **(66)** are readily prepared from their corresponding chalcones **(67)** via the corresponding chalcone epoxide. The cytotoxic pyrazole were synthesised via the epoxide intermediate **(68)**. We have synthesised a large number of aryl-1, 2-azoles by this rout with moderate yield (SCHEME 18).

The reactions of acetylenic ketones with hydrazines have been frequently used to synthesize pyrazole derivatives but the use of acetylenic aldehyde was rare. Recently, Metin Zora et al. developed a method for the synthesis of ferrocenyl pyrazoles **(69)** by the reaction of 3-ferrocenylpropynal **(70)** with hydrazinium salts since it provides easy asses to ferrocenyl pyrazoles **(69a)**and/or **(69b)** (SCHEME 19)[22].

CONCLUSIONS

In conclusion, the review presents an overview of the different developments and the strategies towards the synthesis of important chemical moiety, namely, aryl-1, 2-azoles and its various analogues. Since the aryl-1, 2-azoles and its analogues are bioactive compounds, this microreview will be more informative and helpful to the chemist working in the field of pharmaceutical industries.

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REFERENCES

[1] J.Elguero; 'Comprehensive Heterocyclic Chemistry', A.R.Katritzky, C.W.Rees, E.F.V.Scriven, Eds.; Pergamon: Oxford, **5**, **(1996)**.

[2] **(a)** A.N.Kost, I.I.Grandberg; Adv.Heterocycl.Chem., **6**, 347 **(1996)**.
(b) C.Wiles, P.Watts, S.J.Haswell, Organic Process Research and development, **8**, 28 **(2004)**.

[3] **(a)** V.K.Aggarwal, J.de Vicente, R.V.Bonnert; J. Org.Chem., **68**, 5381 **(2003)**.
(b) B.A.Bhat, S.C.Puri, M.A.Qurishi, K.L.Dhar, G.N.Qazi; Synth.Commun., **35**, 1135 **(2005)**.
(c) B.C.Bishop; Synthesis., **1**, 43 **(2004)**.
(d) M.S.Ahmed, K.Kobayashi, A.Mori; Org.Lett., **7**, 4487 **(2005)**.

[4] S.T.Heller, S.R.Natarajan; Org.Lett., **8**, 2675 **(2007)**.

[5] **(a)** A.Suzuki, A.J.Organomet; Chem., **576**, 147 **(1999)**.
(b) N.Miyaura, A.Suzuki; Chem.Rev., **95**, 2457 **(1995)**.

[6] **(a)** J.Regan, S.Breitfelder, P.Cirillo, T.Gilmore, A.G. Graham, E.Hickey, B.Klaus, J.Madwed, M.Moriak, N.Moss, C.Pargellis, S.Pav, A.Proto, A.Swinamer, L.Tong, C.Torcellini; J.Med.Chem., **45**, 2994 **(2000)**.
(b) Suzuki reaction on N-Boc derivative: PTC WO 03/051797.
(c) M.Patel, J.D.Rodgers, R.J.McHugh, B.L. Johnson, B.C.Cordova, R.M.Klabe, L.T.Bacheler, Erickson-S.Viitanen, S.Ko; Bioorg.Med.Chem. Lett., **9**, 3217 **(1999)**.

[7] X.Wang, J.Tan, K.Grozinger; Tetrahedron Lett., **41**, 4713 **(2000)**.

[8] J.Zhang, S.Didierlaurent, M.Fortin, D.Lefrancois, E.Uridat, V.J.Paul; Bioorg.Med.Chem.Lett., **10**, 2571 **(2000)**.

[9] M.G.Organ, S.Mayer; J.Comb.Chem., **5**, 11 **(2003)**.

[10] C.A.Dvorak, D.A.Rudolph, S.Ma, N.I.Carruthers; J.Org.Chem., **70**, 4188 **(2005)**.

[11] C.Wiles, P.Watts, S.J.Haswell; Organic Process Research & development, **8**, 28 **(2004)**.

[12] J.Zhang, S.Didierlaurent, M.Fortin, D.Lefrancois, E.Uridat, V.J.Paul; Bioorg.Med.Chem.Lett., **10**, 2571 **(2000)**.

[13] A.Schmidt, T.Habeck, M.K.Kindermann, M. Nieger; J.Org.Chem., **68**, 5977 **(2003)**.

[14] S.T.Heller, S.R.Natarajan; Org.Lett., **8**, 2675 **(2006)**.

[15] E.J.Brnardic, R.M.Garbaccio, M.E.Fraley, E.S. Tasber, J.T.Steen, K.L.Arrington, V.Y.Dudkin, G.D. Hartman, S.M.Stirdivant, B.A.Drakas, K.Rickert, E.S. Walsh, K.Hamilton, C.A.Buser, J.Hardwick, W.Tao, S.C.Beck, X.Mao, R.B.Lobell, L.Sepp-Lorenzino; Bioorg.Med.Chem.Lett., **17**, 5989 **(2007)**.

[16] F.E.Boyer, J.V.N.Vara Prasad, A.L.Choy, Louis Chupak, M.R.Dermyer, Q.Ding, M.D.Huband, W. Jiao, T.Kaneko, V.Khlebnikov, Ji-Young Kim, M.S. Lall, S.N.Maiti, K.Romero, X.Wu; Bioorg. Med. Chem.Lett., **17**, 4694 **(2007)**.

[17] Y.Tong, M.Przytulinska, Zhi-Fu Tao, J.Bouska, K.D.Stewart, C.Park, G.Li, A.Claiborne, P.Kovar, Z.Chen, P.J.Merta, Mai-Ha Bui, A.Olson, D. Osterling, H.Zhang, H.L.Sham, S.H.Rosenberg, T.J. Sowin, Nan-horng Lin; Bioorg.Med.Chem.Lett., **17**, 5665 **(2007)**.

[18] P.Diana, A.Carbone, P.Barraja, A.Martorana, O.Gia, L.Dallavia, G.Cirrincione; Bioorg.Med.Chem.Lett., **17**, 6134 **(2007)**.

[19] T.Persson, J.Nielsen; Org.Lett., **8**, 3219 **(2006)**.

[20] M.L.James, R.R.Fulton, D.J.Henderson, S.Eberl, S.R.Meikle, S.Thomson, R.D.Allan, F.Dolle, M.J. Fulham, M.Kassiou; Bioorg.Med.Chem., **13**, 6188 **(2005)**.

[21] R.LeBlanc, J.Dickson, T.Brown, M.Stewart, H.N. Pati, D.VanDerveer, H.Arman, J.Harris, W. Pennington, H.L.Holt, Jr, M.Lee; Bioorg.Med. Chem., **13**, 6025 **(2005)**.

[22] M.Zora, A.N.Pinar, M.Odabasoglu, O. Buyukgungor, G.Turgut; J.Organomet.Chem., **693**, 145 **(2008)**.