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Eco-friendly and Expedient Synthesis of Benzofuran based 1, 3, 5-Substituted Pyrazole Derivatives

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Abstract

An efficient and convenient synthesis ofbenzofuran based 1,3,5-substituted pyrazole analogues has been achieved by2-acetyl benzofuran on reaction with various aromatic aldehydes in presence of Zirconium chloride as greener catalyst affords benzofuran chalcones;(E)-1-(5-substituted benzofuran-2-yl)-3-(4-substituted phenyl)prop-2-en-1-one;this on treatment with hydrazine hydrate /phenyl hydrazine in the presence of DABCO (1,4-diazabicyclo[2.2.2] octane) as an eco-friendly catalyst and using the solvent-drop grinding method gives corresponding pyrazole.The structure of the synthesized compounds was elucidated using spectroscopic techniques (IR, NMR and Mass).

Introduction:

Benzofuran derivatives attracted due to their valuable biological activities including anticancer, antimicrobial, immune modulatory, neuroprotective, antioxidant and anti-inflammatory properties [1-4]. The cyclopean [b] benzo furan silvestrolis a very potent cytotoxic natural product against several human cancer cell lines [5,6]. Benzo furans with substituents at C-2 and C-3 positionshave been extremely investigated for their biological and pharmacological properties [7-9], antimicrobial activities [10]. Recently, there are many studies related to the cytotoxic activity of chalcones derivatives in various cancer cell lines [11-14]. Since then many studies have focused on structural modifications of the chalcone scaffold and the variety of its biological activities [15-16]. A number of synthetic modifications, such as heterocyclic infused [17], biphenyl based [18], coumarin based chaconnes [19] or other substitutions [20-24], have also been reported to affect the biological activities including anticancer activities of chaconnes [25-27].

Pyrazole scaffold represents a common motif in many pharmaceutical active and remarkable compounds demonstrating a wide range of pharmacological activities; the most important activities are the anti-inflammatory, antibacterial, antifungal, hypoglycemic and anti-hyperlipidemia.[28,29],the pyrazine ring represent an advantageous choice for the synthesis of pharmaceutical compounds with different activities and good safety profiles.[30-32]The literature survey approaching to synthesis of amide linkedpyrazole gathered with benzo furan moiety indicate the lack of reference available. Over the past decade, zirconium compounds have been found an ever increasing role in organic synthesis, which has been recognized by a number of excellent review articles and books covering various aspects of zirconium compounds as catalysts or reagents in synthetic organic chemistry[33-39].1,4-diazabicyclo [2.2.2]octane (DABCO) has been used in many organic preparations as a good solid catalyst. DABCO has received considerable attention as an inexpensive, ecofriendly, high reactive, easy to handle and non-toxic base catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity.[40].In the present work, two step synthetic strategies were employed for the preparation of benzo furan based 1,3,5-substituted pyrazole derivatives .In the first step, (E)-1-(5-substituted benzofuran-2-yl)-3-(4-substituted phenyl)prop-2-en-1-onewas prepared by using 2-acetyl 5-substituted benzo furans and different aromatic aldehydes in presence of solid green catalyst $ZrCl_4$, further these chaconnes on treatment with hydrazine hydrate /phenyl hydrazine with DABCO as ecofriendly catalyst affords 3-(5-substituted benzofuran-2yl)-5-

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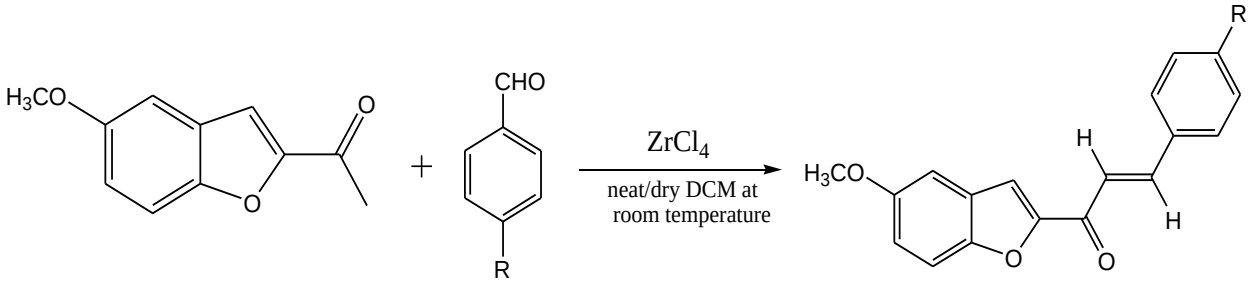
(4-substitutedphenyl)4,5-dihydro-1-phenyl/-1H-pyrazole. 2. **Material and Methods:** Melting points were determined in open capillaries in paraffin bath and are uncorrected. TLC analysis was performed on silica gel and spotting was done using iodine or UV light. IR spectra were recorded on Perkin - Elmer model 446 instruments in KBr phase. ^{1}H NMR was recorded in $CDCl_3$/DMSO-d6 using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on LCM Spectrometer.

3. Experimental:

1) Synthesis of (E)-1-(5-substituted benzofuran-2-yl)-3-(4-substituted phenyl) prop-2-en-1-one: aromatic aldehydes (5.0 mmol) and 2-acetyl-5-methoxy benzo furan(5.0mmol) were mixed together and then anhydrous $ZrCl_4$ (46.6 mg, 25mol%) was added and the solution stirred at room temperature under an air atmosphere for 40 min. After the completion of the reaction (monitored by TLC (AcOEt/PE) , the crude mixture was worked up in ice and then extracted with ethyl acetate solution (3×10 mL).The combined ethyl acetate extract was dried over anhydrous Na_2SO_4,filtered and then concentrated in vacuum, and the resulting product was purified by simple crystallization in ethanol to afford the pure product as a yellowish solid (78 % yield).In critical case if when one or both the reactants are solid we have used 1–2 ml of dry DCM, i.e. minimal amount of solvent required to dissolve the solid reactant and make the reaction feasible. Except this all methodology used is same as mentioned above. All the synthesized compounds were characterized by their spectroscopic data .The compounds that are known are identified by comparison of their spectroscopic data with those reported in the literature.

Reaction:



Where, R= H,Br,Cl, NO_2, CH_3, OH, NH_2, C_6H_5, OCH_3 and Cinnamaldehyde.(Compound 1a-1j)

Characterization:1]*(2E)-1-(5-methoxy-1-benzofuran-2-yl)-3-phenylprop-2-en-1-one(1a)*Yellowish solid ,72% yield, m.p. 205–207 ^{o}C ,FT-IR(KBr,cm^{-1}):1665(C=O),1589(C=C);^{1}H-NMR(400MHz,DMSO-d6),δppm:8.71(s,1H,5-H),7.90(s,1H,7-H),7.42-7.44(m,4H,H-13,H-17,H-11,H-10)7.24-7.45(m,2H,H-2,H-3),7.25–7.30(m,3H,14-H,15-H,16-H),3.45(3H,OCH_3ofbenzofuran), MS:m/z=278(M^+)**2]*(2E)-1-(5-methoxy-1-benzofuran-2-yl)-3-(3-bromophenyl)prop-2-en-1-one(1b)*.** Pale yellowish solid ,74% yield, m.p. 185–187^{o}CFT-IR(KBr,cm^{-1}):1634(C=O),1589(C=C);^{1}H NMR(400MHz,DMSO-d6),δppm:7.71(s,1H,H-5),8.24(s,1H,H-7),7.91-8.15(m,8H,H-3,H-2,H-17,H-16,H-14,H-13,H-10,H-11),3.25(3H,$OCH_3$of benzofuran),MS:m/z=356(M^+)**3]*(2E)-1-(5-methoxy-1-benzofuran-2-yl)-3-(3-chlorophenyl)prop-2-en-1-one(1c)*.** Faint brown solid ,75% yield, m.p. 156–157 ^{o}CFT-IR(KBr,cm^{-1}):1666 (C=O),1647 (C=C);^{1}H-NMR (400MHz,DMSO-d6), δppm:8.02 (s,1H,5-H),8.13(s,1H,7-H),8.01-7.48(m,8H,3-H,2-H,17-H,16-H,14-H,13-H,10-H,11-H),3.15(3H,OCH_3ofbenzofuran),MS:m/z=312(M^+)**4]*(2E)-1-(5-methoxy-1-benzofuran-2-yl)-3-(3-nitrophenyl)prop-2-en-1-one(1d)***.Yellowish solid ,79 % yield, m.p. 215–217^{o}C ,FT-IR(KBr,cm^{-1}):1710(C=O),1687(C=C);^{1}H-NMR(400MHz,DMSO-d6),δppm:8.66(s,1H,5-H),8.92(s,1H,7-H),7.97-6.88(m,8H,3-H,2-H,17-H,16-H,14-H,13-H,10-H,11-H),3.45(3H,OCH_3ofbenzofuran), MS:m/z=323(M^+)

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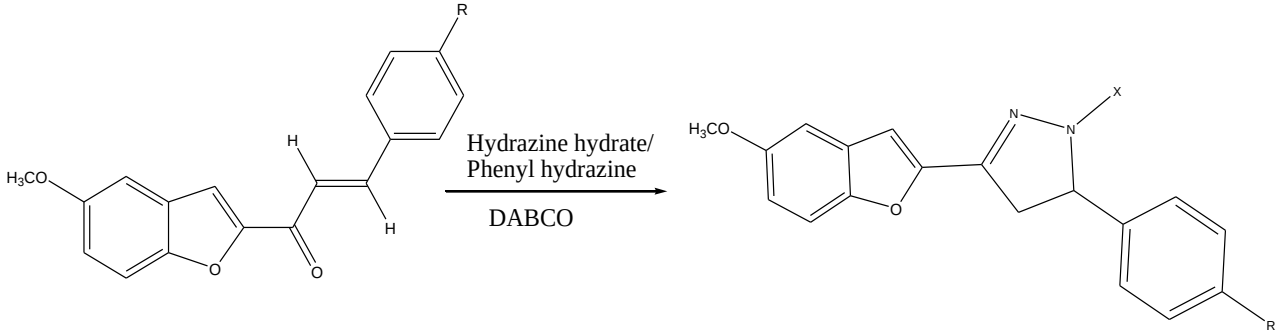
5]*(2E)-1-(5-methoxy-1-benzofuran-2-yl)-3-(3-methylphenyl)prop-2-en-1-one(1e)*Paleyellowish solid,64% yield, m.p. 187–188ºCFT-IR(KBr,cm^{-1}):1674 (C=O),1622 (C=C);^{1}H-NMR (400MHz,DMSO-d6), δppm: 7.61 (s,1H, 5-H),7.52(s,1H,7-H), 2.21(s,3H,9-H)7.77-6.58 (m,8H,3-H,2-H,17-H,16-H,14-H,13-H,10-H,11-H)3.15(3H,OCH_3ofbenzofuran),MS:m/z=292(M^+)**2) Synthesis of3-(5-substituted benzofuran -2yl)-5-(4-substituted phenyl)4,5-dihydro-1-phenyl/-1H-pyrazole from (E)-1-(5-substituted benzofuran-2-yl)-3-(4-substituted phenyl) prop-2-en-1-one:(Compound 2a-2j)** A mixture of (E)-1-(5-substituted benzofuran-2-yl)-3-(4-substituted phenyl) prop-2-en-1-one (2 mmole) and Phenyl hydrazine /hydrazine hydrate (2 mmole)were taken in mortar at room temperature. A catalytic amountof DABCO was added. The reaction mixture was ground by the pestle, for 30 min.The reaction mixture was then poured into cold water, and the solid product was collected by filtration. The crude product was recrystallized from ethanol as brown crystals.(72 % yield).All the synthesized compounds were characterizedby their spectroscopic data.

Reaction:



If reactant isHydrazine hydrate then in product X= H, if phenyl hydrazine then X=C_6H_5
R= H,Br,Cl, NO_2, CH_3, OH, NH_2, C_6H_5, OCH_3 and Cinnamaldehyde (Compound 2a-2j)**Characterization:1)4,5-dihydro-3-(5-methoxybenzofuran-2-yl)-5-p-tolyl-1HpyrazoleX=H (2e):** Palebrown solid,68% yield, m.p. 157–158ºCFT-IR(KBr,cm^{-1}):1587(C=N),1076-1088(C-O-C)^{1}H-NMR(400MHz,$CDCl_3$), δ ppm:7.94 (s,1H,Pyrazole-H),7.32(d,1H,C7-H),7.31(d,1H,C4-H)7.17(dd,1H,C6-H),7.20-6.68(m,5H,phenylAr-H),6.53(s,1H,FuranH),5.88(m,1H,C5-H of pyrazole),3.77(m,1H,C4-Hof pyrazole),3.62 (m,1H,C4-H of pyrazole),3.07(3H,$OCH_3$of benzofuran)MS:m/z=306(M^+)

2)4,5-dihydro-3-(5-methoxybenzofuran-2-yl)-5-(4-nitrophenyl)-1H-pyrazoleX=H(2d): Paleyellow solid,73% yield, m.p. 117–118ºCFT-IR(KBr,cm^{-1}):1610(C=N),1086-1098(C-O-C)^{1}H-NMR (400MHz,$CDCl_3$), δ ppm: 7.98 (s,1H,Pyrazole-H),7.62(d,1H,C7-H), 7.61(d,1H,C4-H)7.37(dd,1H,C6-H),6.73(s,1H,FuranH),7.40-6.88(m,5H,phenylAr-H),5.98(m,1H,C5-H of pyrazole),3.87(m,1H,C4-H of pyrazole),3.52(m,1H,C4-H of pyrazole)3.17(3H,$OCH_3$of benzofuran), MS:m/z=337(M^+)

3)4,5-dihydro-3-(5-methoxybenzofuran-2-yl)-1-phenyl-5-p-tolyl-1H-pyrazoleX=H(2a): Pale red soild,64% yield, m.p.189–190ºCFT-IR(KBr,cm^{-1}):1622(C=N),1096-1108(C-O-C)^{1}H-NMR:(400MHz,$CDCl_3$),δppm:7.62(d,1H,C7-H),7.61(d,1H,C4-H)7.37(dd,1H,C6-H),6.73(s,1H,FuranH),7.36-6.88(m,5H,phenylAr-H),5.88(m,1H,C5-Hofpyrazole),3.77(m,1H,C4-Hofpyrazole),3.62(m,1H,C4-Hofpyrazole)3.17(3H,$OCH_3$of benzofuran),2.27(3H,$CH_3$of benzene ring)MS:m/z=306(M^+)

4)5-(4-chlorophenyl)-4,5-dihydro-3-(5-methoxybenzofuran-2-yl)-1-phenyl-1H-pyrazole X=C_6H_5(3k) Pale yellow soild,62% yield, m.p.124–126ºCFT-IR(KBr,cm^{-1}):1629(C=N),1106-1116(C-O-C)^{1}H-NMR:(400MHz,$CDCl_3$),δppm:7.76(d,1H,C7-H),7.71(d,1H,C4-H)7.27(dd,1H,C6-H),6.13(s,1H,FuranH),7.36-6.08(m,10H,phenylAr-H),5.16(m,1H,C5-Hof pyrazole),3.55(m,1H,C4-

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Hofpyrazole),3.17(m,1H,C4-Hofpyrazole)3.07(3H,$OCH_3$of benzofuran),2.17(3H,$CH_3$of benzene ring)MS:m/z=402(M^+)

5)5-(4-bromophenyl)-4,5-dihydro-3-(5-methoxybenzofuran-2-yl)-1-phenyl-1H-pyrazole Colorless soild,66% yield, m.p.181–182°CFT-IR(KBr,cm^{-1}):1640(C=N),1116-1126(C-O-C)^{1}H-NMR:(400MHz,$CDCl_3$),δppm:7.96(d,1H,C7-H),7.81(d,1H,C4-H)7.37(dd,1H,C6-H),6.23(s,1H,FuranH),7.56-6.28(m,10H,phenylAr-H),5.36(m,1H,C5-Hof pyrazole),3.76(m,1H,C4-Hofpyrazole),3.57(m,1H,C4-Hofpyrazole)3.47(3H,$OCH_3$of benzofuran),2.37(3H,$CH_3$of benzene ring)MS:m/z=446(M^+)

4. Result and discussion:

The structures of all synthesized compounds were elucidated using spectroscopic analysis (IR, NMR, and Mass). Our initial investigations were concerned the zirconium chloridecatalyzed aldol reaction of benzaldehyde with 2-acetyl-5-methoxybenzofuransas a model system. We chose this system in order to optimize the reaction conditions in terms of the yield, time and reaction temperature.

Table 1
Effect of catalyst loading on the synthesis of (E)-1-(5-substituted benzofuran-2-yl)-3-(4-substituted phenyl) prop-2-en-1-one[a,b]

Entry	$ZrCl_4$ (mol %)	Solvent	Time (h)	Yield(%)
1	30	Ethanol	2 hr	45
2	20	DCM	1.5 hr	64
3	15	$CHCl_3$	1.5 hr	59
4	05	CH_3CN	2 hr	56
5	25	Neat	40 min	72

a Reaction conditions: benzaldehyde reacted with benzofurans in presence of $ZrCl_4$ at room temperature.(for compound 1a)
bIsolated yield (%).

Present methodology works efficiently with a wide varietyof substrates. In most cases the reaction proceeded smoothlyto produce the corresponding chalcones.

The proposed mechanism of $ZrCl_4$ catalyzed reaction mayproceed, through the enolate intermediate generated via the initial addition of zirconium chloride to the carbonyl carbon of aryl ketone.It was proposed that Zr^{4+}coordinate with the carbonyl oxygen of the ketone and form ancolored transition metal complex (this color varied accordingly the aryl ketone was used), it generates the enolate intermediate by the abstraction of proton from the α-carbon of the aryl ketone.

5.Conclusions:

In conclusion, we have successfully developed a simple,efficient and greener methodology to prepare a wide variety of 1,3-diaryl-2-propenones using zirconium chloride in catalytic amounts; and this on treatment with hydrazine /phenyl hydrazine in presence of green catalyst DABCO affords 1,3,5-Substituted pyrazole derivatives.This method can be sustained by the less reaction time as well as high product yields. This protocol is the environmentally acceptable, economical and solvent less process for the described synthesis.

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