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HIGHLY EFFICIENT MICROWAVE ASSISTED SYNTHESIS OF 2-BENZOYL-3-METHYLBENZO[4,5]IMIDAZO[2,1-b]THIAZOLE

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ABSTRACT: The synthesis of 2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thiazole derivatives have been designed in the presence of glycerol as a green medium. The synthesis begins with the reaction of mercaptobezimidazole and aromatic ketones in a glycerol to offer 2-((1H-benzo[d]imidazol-2-yl)thio)-1-phenylethanone. The resulting intermediate is further reacted with acetic anhydride to achieve final 2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thiazoles. The present protocols have various features such as appreciable yield, environmentally benign, enhance reaction rate and avoid toxic metal catalyst and volatile hazardous solvents.

KEYWORDS: Imidazo[2,1-b][1,3,4]thiadiazole, benzoic acid, glycerol-water, phenacyl bromide

INTRODUCTION

Sulphur and nitrogen containing heterocycles have attracted great interest in medicinal and drug chemistry due to their wide bioactivities and structural versatility. Among these, Benzothiazoles are mostly reported for their exceptional antibacterial, antitumor, antiviral, anti-inflammatory, and enzyme inhibitory properties [i-iv]. The combination of benzimidazole with thiazole nucleus form benzo[4,5]imidazo[2,1-b]thiazoles, has attracted attention as a strategy to enhance pharmaceutical profiles and structural diversity [v-vii].

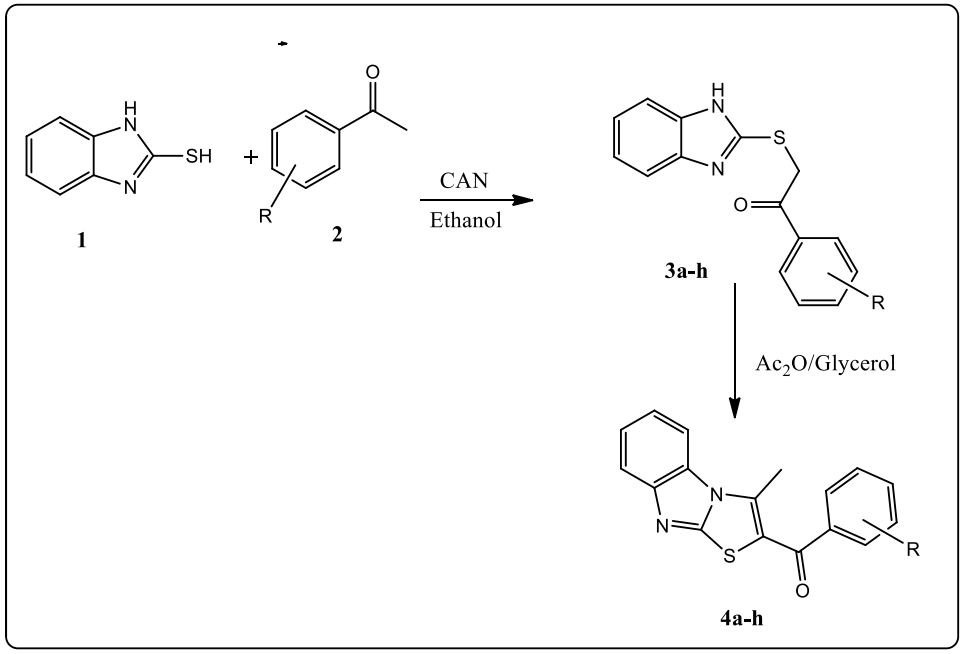
Literature focus on the synthetic perspective, benzo[4,5]imidazo[2,1-b]thiazoles can be achieved through the coupling of 2-mercaptobenzimidazole with carbonyl compounds or via oxidative cyclization of appropriate precursors[viii-ix]. 2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thiazole is of particular interest as a lead scaffold for further biological evaluation and synthetic exploration.

benzo[4,5]imidazo[2,1-b]thiazoles are valuable subclass of fused heterocycles, combining the benzimidazole and thiazole scaffold enhance electronic and structural binding activity to organic receptor.

In particular, benzo[4,5]imidazo[2,1-b]thiazoles have evolve as an important fused heterocyclic system due to their rigid, electron-rich structure and valuable medicinal properties. These scaffolds have been associated with diverse the combined pharmacophoric properties

biological activities, including antimicrobial, anticancer, anti-inflammatory, and enzyme inhibitory effects[x-xii].

Glycerol is non-volatile, biodegradable, and nontoxic and by product of biodiesel manufacture; its easy availability have made it acceptable green alternative to conventional organic solvents. Moreover, glycerol provide catalyst reuse and it supports metal-catalyzed, metal-free, and enzymatic reactions procudures [xiii-xvi].



Scheme 1 Synthesis of 2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thiazoles

Experimental

Material and method

General method for preparation of 6-substituted-2-benzoyl-3methylbenzimidazo[2,1-b]thiazoles ***4(a–h)***

Ceric ammonium nitrate 2 mol % was added into the mixture of 2-mercaptobenzimidazoles (1.0 mmol) and acetophenone (1.0 mmol) in glycerol and irradiated under microwave for 1 min to achieved 2-((1H-benzo[d]imidazol-2-yl)thio)-1-phenylethanone as intermediate. Next, 2-((1H-benzo[d]imidazol-2-yl)thio)-1-phenylethanone irradiated with acetic anhydride (1.0 mmol) for 3-4 min. until completion, monitored by TLC using ethyl acetate-n-hexane (30:70, v/v). The reaction mixture was neutralized with aqueous sodium bicarbonate and obtained solid product was recrystallized using ethanol and dried to yield pure products.

Results and Discussion

The synthesis of **2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thiazole** was accomplished via a two-step sequence starting from 2-mercaptobenzimidazole and acetophenones. In the first step, condensation of 2-mercaptobenzimidazole with acetophenone afforded the intermediate 2-((1H-benzo[d]imidazol-2-yl)thio)-1-phenylethanone via nucleophilic substitution at the sulphur atom. Subsequent cyclization under acidic conditions yielded the desired fused heterocycle in good yield.

Synthesis of 2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thaizole initially tried by using various polar solvents such as water, ethanol, propane-2-ol and glycerol. Reaction could proceed in all these solvents but significant yield was obtained in glycerol therefore glycerol is the better choice of medium for present protocol. **(Table 1)**

Table 1: Effect of solvents on the synthesis of 2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thaizole (4a)

Solvent	Microwave Power	Time	Yield
Water	180	12	64
Ethanol	200	10	82
Propane-2-ol	200	08	80
Glycerol	100	04	93

To generalized the scope of the present method variously substituted 2-((1H-benzo[d]imidazol-2-yl)thio)-1-phenylethanone cyclized in the presence of acetic anhydride under microwave to achieved substituted 2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thaizoles. The results are depicted in **table 2.** The reaction proceeded smoothly and afforded the target compound as a crystalline solid, which was purified by recrystallization. The structure of the compound was confirmed using spectral and elemental analyses.

Table 2 effect of substituents on the yield of the reaction

Compounds	Time(minutes)	Yield	Melting Points
4a	3 min. 30 sec	93	123-125
4b	3 min.30 sec	92	204-205
4c	4min.10 sec	91	203-204
4d	3min.40sec	94	244
4e	3min.35sec	92	102
4f	3 min.10 sec	93	169
4g	3min.20sec	92	165

The IR spectrum displayed a strong absorption band at **1670 cm^{-1}**, confirming the presence of the benzoyl **C=O** group. The **^{1}H NMR spectrum** showed a singlet at δ **2.45 ppm**, corresponding to the 3-methyl group, along with multiplets in the δ **7.2–7.9 ppm** region for aromatic protons, and a downfield singlet at δ **8.12 ppm**, assigned to the imidazole proton. The **^{13}C NMR spectrum** was consistent with the aromatic carbons, carbonyl, and heteroaryl carbons. The **mass spectrum** exhibited a molecular ion peak at **m/z 292**, consistent with the calculated molecular weight.

Conclusion

In summary, **2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thiazole** was successfully synthesized through the condensation of 2-mercaptobenzimidazole with acetophenones, followed by cyclization. The compound was obtained in good yield and its structure was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis. The present methods have several advantages over reported protocols such as rapid, environmentally benign, inexpensive and offers excellent yield.

Spectral data of synthesized compounds

2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-b]thiazole (4a). IR (KBr, cm−1): 1686 (C=O); ^{1}H NMR (400 MHz, DMSO-d6) d (ppm) 8.04–8.01 (d, 1H, 3 J = 8.0 Hz, 4H), 7.86–7.85 (m, 2H, 20 ,60 -H), 7.75–7.71 (m, 2H, 40 ,7H), 7.62–7.59 (m, 2H, 30 ,50 -H), 7.45–7.42 (m, 1H, 6H), 7.34– 7.31 (m, 1H, 5H), 2.74 (s, 3H, 3-CH3); 13C NMR (101 MHz) d (ppm) 189.4, 154.6, 148.6, 139.8, 138.78, 133.5, 130.6, 129.4, 129.6, 125.1, 122.5, 121.7, 119.4, 113.6, 15.6; anal. calcd. for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58% found: C, 69.80; H, 4.11; N, 9.53%.

2-(4-Fluorobenzoyl)-3-methylbenzo[4,5]imidazo[2,1-b]thiazole (4b). IR (KBr, cm−1): 1674(C=O); ^{1}H NMR (400 MHz, DMSO-d6) d (ppm) 8.04–8.03 (d, 1H, 3 J = 8.0 Hz, 4H), 7.95–7.91 (m, 2H), 7.74–7.72 (d, 1H), 7.45–7.42 (m, 3H), 7.34–7.31 (m, 1H), 2.74 (s, 3H, -

CH_3); ^{13}C NMR (101 MHz) d (ppm) 186.7, 165.6, 166.1, 153.5, 147.7, 138.1, 134.2 (d), 132.3 (d), 131.4, 131.6, 125.2, 122.4, 121.2, 119.4, 116.3, 116.5, 113.3, 15.8.

2-(4-Methylbenzoyl)-3-methylbenzo[4,5]imidazo[2,1-b]thia zole (4e). IR (KBr, cm−1): 1682 (C=O);1HNMR(400MHz,DMSO-d6)d(ppm) 8.01–7.98 (d, 1H, 3J = 8.1 Hz, 4H), 7.75–7.73 (m, 2H, 20,60-H), 7.73–7.71 (d, 1H, 3J = 8.0 Hz, 7H), 7.45–7.38 (m, 3H, 30,50,6H), 7.34–7.27 (m, 1H, 5H), 2.73 (s, 3H, 40-CH3), 2.43 (s, 3H, 3-CH3); 13C NMR (101 MHz) d (ppm) 188.6, 154.6, 148.5, 144.1, 139.5, 135.8, 130.7, 129.7, 129.6, 124.7, 121.6, 121.4, 119.2, 113.6, 21.9, 15.5; anal. calcd. for C18H14N2OS: C, 70.56; H, 4.61; N, 9.14% found: C, 70.51; H, 4.55; N, 9.10%.

2-(4-Methoxylbenzoyl)-3-methylbenzo[4,5]imidazo[2,1-b] thiazole (4f) ^{1}H NMR (400 MHz, DMSO-d6) d (ppm) 8.05–8.03 (d, 1H, 3J = 8.0 Hz, 4H), 7.90–7.86 (d, 2H, 3J = 8.7 Hz, 20,60-H), 7.74–7.72 (d, 1H, 3J = 8.0 Hz, 7H), 7.45–7.41 (t, 1H, 3J = 8.0 Hz, 6H), 7.34–7.30 (t, 1H, 3J = 8.0 Hz, 5H), 7.13–7.11 (d, 2H, 3J = 8.7 Hz, 30,50-H), 3.89 (s, 3H, 40-OCH3), 2.77 (s, 3H, 3-CH3); 13C NMR(101MHz)d(ppm)187.5, 163.7, 154.6, 148.5, 138.4, 132.7, 130.4, 124.7, 121.5, 121.6, 119.3, 114.7, 113.7, 56.3, 15.9; anal. calcd. for C18H14N2O2S: C, 67.06; H, 4.38; N, 8.69% found: C, 67.01; H, 4.33; N, 8.61%

3-Methyl-(2-(2-thiophen)oyl)-benzo[4,5]imidazo[2,1-b]thiazole (4h).

^{1}HNMR(400MHz,DMSO-d6)d(ppm) 8.19–8.17 (dd, 1H, J =5.2 Hz, J=1.1Hz,30-H), 8.09–8.06 (m, 2H, 4,50-H), 7.78–7.73 (d, 1H, 3J = 8.0 Hz, 7H), 7.46–7.45 (m, 1H, 6H), 7.36–7.30 (m, 2H, 5,40-H), 2.98 (s, 3H, 6-CH3); 13C NMR (101 MHz) d (ppm) 179.7, 154.4, 148.8, 143.5, 139.3, 136.6, 135.8, 130.9, 129.5, 125.5, 122.8, 119.3, 118.6, 113.6, 15.4; anal. calcd. for C15H10N2OS2: C, 60.38; H, 3.38; N, 9.39% found: C, 60.30; H, 3.33; N, 9.35%.

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Conflict of interest Authors do not have any conflict and financial interest

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