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Sulphanilic Acid촉매하에서 벤질/벤조인과 방향족 알데히드로부터 2,4,5-Triarylimidazoles의 간편한 One-pot 합성

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Sulphanilic Acid Catalyzed Facile One-pot Synthesis of 2,4,5-Triarylimidazoles From Benzil/Benzoin and Aromatic Aldehydes

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요 약. Sulphanilic Acid 촉매를 사용한 벤조인 또는 벤질, 초산암모늄 그리고 방향족 알데히드의 축합반응을 통한 간단하고 높은 수율의 2,4,5-Triarylimidazoles의 One-pot 합성에 대한 보고 값싼 가격의 촉매,높은 수율 그리고 짧은 반응 시간은 제시된 방법의 장점이다.

주제어: 술파닐산, Triarylimidazoles, 벤조인, 벤질, 초산 암모늄, 방향족 알데히드

ABSTRACT. A simple and high yielding one-pot method for synthesis of 2,4,5-triarylimidazoles from condensation of benzoin or benzil, ammonium acetate and aromatic aldehydes using sulphanilic acid catalyst is described. The lower priced catalyst, higher yields and shorter reaction time are the advantages of the presented method.

Keywords: Sulphanilic Acid, Triarylimidazoles, Benzoin, Benzil, Ammonium Acetate, Aromatic Aldehydes

INTRODUCTION

Triarylimidazole compounds have gained the remarkable importance due to their widespread biological activities and their use synthetic chemistry. The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds. For example, the amino acid histidine, the hypnotic agent etomidate,[1] the antiulcerative agent cimetidine,[2] the proton pump inhibitor omeprazole,[3] the fungicide ketoconazole,[4] and the benzodiazepine antagonist flumazenil[5] are imidazole derivatives. In recent years, substituted imidazoles are substantially used in ionic liquids,[6] that has been given a new approach to 'Green Chemistry'. In addition, they are used in photography as photosensitive compound.[7] Literature survey reveals the several methods for synthesizing them, mainly using nitriles and esters [8-10] as the starting substrates. Japp and Radziszewski proposed the first synthesis of theimidazole core in 1882, starting from 1,2-dicarbonyl compounds aldehydes and ammonia, to obtain 2,4,5-triphenylinidazoles.[11,12] Subsequently, many other syntheses of this important heterocycle have been published.[13] For example, 2,4-diaryl-1*H*-imidazoles are often obtained from amidines and R-bromo arylketones.[14] Moreover, Zhang and Chen described an efficient procedure to obtain unsymmetrical, C5 unsubstituted 2,4-diarylimidazoles. In

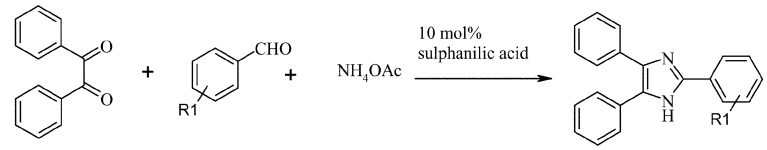
this approach acetophenones are oxidized *in situ* to R-tosyloxyacetophenones, which then condense with arylamidines to obtain the desired compounds.[15] Recently, ionic liquids like (Hbim)BF_4 were used for the synthesis of theses compounds in a very short reaction time.[16] Also, the microwave-assisted solid-phase synthetic methods were reported for synthesis of 2,4,5-trylimidazoles using benzil or *N*-hydroxybenzil, ammonium acetate and aldehydes.[17,18] However, some of theses previous methods have suffered from one or more drawbacks like high temperature requirement, highly acidic conditions, and the use of metal cyanides for preparation of the nitrile compounds that limit their uses.[19,20] Some of methods have resorted to harsh conditions (e.g. the formamide synthesis, which requires excess reagents, H_2SO_4 as a condensing agent, 150-200 °C, 4-6 h, 40-90%).[21-23] Therefore, the development of mild, efficient and versatile method is still strongly desirable. Herein, we have presented a novel, mild and efficient method for synthesis of 2,4,5-triarylimidazole using sulphanilic acid catalyst. Out of range of acid catalysts, sulphanilic acid has attracted much attention because of its suitable acidity, eco-friendliness, easy availability and low cost.

RESULTS AND DISCUSSION

Initially, we studied the catalytic efficiency of sulphanilic acid for synthesis of 2,4,5-triphenyl-1*H*-imidazole (**3a**) using benzil, ammonium acetate and benzaldehyde in different solvents and various mol% of sulphanilic acid (*Scheme* 1). The title compound **3a** was isolated with 97% yield using optimized reaction conditions (*Table* 1), (ethanol-water (1:1) solvent and 10 mol% sulphanilic acid catalyst). Using the standardized reaction conditions, a range of 2-aryl-4,5-diphenyl-1*H*-imidazoles were synthesized and results were summarized in *Table* 2. From the results obtained, the aldehydes with electron-donating substituents favor the reaction and it was completed within the shorter reaction

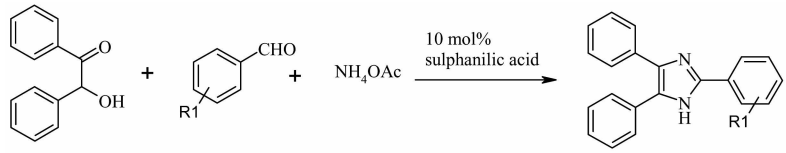
Table 1. Optimization of reaction conditions and mol% of sulphanilic acid for the synthesis of 1-methylphenyl-2-phenyl-1*H*-benzimidazoles

Solvent	Mol % of sulphanilic acid	Reaction time (min)	Yield (%)
DCM	20	65	82
THF	20	60	85
Acetonitrile	20	60	68
Ethanol	20	50	86
THF-water (1:1)	20	45	90
Acetonitrile-water (1:1)	20	45	84
Ethanol-water (1:1)	20	45	97
Ethanol-water (1:1)	15	45	97
Ethanol-water (1:1)	10	45	97
Ethanol-water (1:1)	5	60	88
Ethanol-water (1:1)	2.5	75	85



1 2 3a - 3k

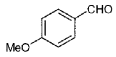
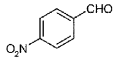
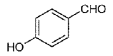
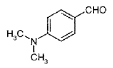
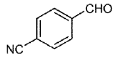
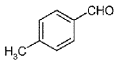
Scheme 1. Synthesis of 2,4,5-triarylimidazoles using benzil, aromatic aldehydes, ammonium acetate and 10 mol% sulphanilic acid catalyst.



4 2 3a - 3k

Scheme 2. Synthesis of 2,4,5-triarylimidazoles using benzoin, aromatic aldehydes, ammonium acetate and 10 mol% sulphanilic acid catalyst.

Table 2. Synthesis 2,4,5-triaryl-1*H*-imidazoles using benzil or benzoin, ammonium acetate, aromatic aldehydes, and 10 mol% sulphanilic acid

Entry	Ar-CHO	Rection time (min)		Yield (%)	
		Benzil	Benzoin	Benzil	Benzoin
3a		45	70	97	93
3b		50	75	95	92
3c		45	75	94	89
3d		70	110	87	66
3e		50	75	95	94
3f		55	70	92	88
3g		60	85	93	86
3h		40	65	96	94
3i		45	70	94	93
3j		50	75	92	77
3k		50	75	95	93

time (*Table* 2, entries 3a, 3h) than the aldehydes with electron-withdrawing substituents (*Table* 2, entry 3d). Especially, for the *p*-nitrobenzaldehyde the (**3d**), the reaction was very slow and also it was the low yielding. The method was found to be effective for hetero-aromatic aldehydes also for the synthesis 2-heteroaryl-4,5-diphenyl-1*H*-imidazoles with better yields (**3i**, **3j** and **3k**). The easy work-up is advantageous aspect of this method, which includes the pouring of the reaction mixture over ice-water to get the precipitation of solid. It could be filtered to give the sufficiently pure compound in good yield. The present method was superior to the available methods in regards with yields and reaction time.[21] Especially, for the preparation of 2-(4-methylphenyl)-4,5-diphenyl-1*H*-imidazole (**3h**) was synthesized in 96% while the reported yield was 74% and also 2-(2-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (**3b**) was synthesized in 95% while the reported yield was 85 %.[25]

1,2-Diketones (like benzil) are usually prepared from the a-hydroxy ketones (like benzoin) catalyzed by various oxidants. Some of these catalysts are toxic, costly and also required the tedious experimental procedures.[26] To avoid the preparation of starting material 1,2-diketones like benzil, the synthesis of 2,4,5-triphenyl-1*H*-imidazole was studied using benzoin. Surprisingly, using the similar reaction conditions, 2,4,5-tripheny-1*H*-imidazole was isolated in 93% yield. Encouraged by this result, we extended the methodology for synthesis of various 2,4,5-triaryl-1*H*-imidazoles using benzoin and various aromatic aldehydes. The yields obtained were in the range of 66% to 94%.

CONCLUSION

Using 10 mol% sulphanilic acid catalyst, 2,4,5-triaryl-1*H*-imidazoles were efficiently synthesized with moderate to excellent yields from benzil and as well as benzoin. For all the presented reactions, the ethanol-water solvent was used which is relatively environmentally benign and supporting to Green Chemistry. The advantages of the reported method are the use of cheap and easily available catalyst, easy work-up, and better yields.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplate (m) and broad (br). Mass spectra were taken with Micromass - QUATTRO-II of WATER mass spectrometer. HPLC was performed using Zorbax SB-C18 reverse phase column (0.46×25 cm) on Shimadzu instrument equipped with an automatic injector with UV-PDA detector. Detection was carried out at 254 nm. The mobile phase consists of 0.05 % TFA and acetonitrile (1:1, V/V). The products were eluted at flow rate of 1 ml/min using isocratic method. Flash column chromatog-

raphy was performed with 300-400 meshes silica gel and analytical thin layer chromatography was performed on precoated silica gel plates (60F-254) with system (v/v) indicated. Melting points were determined in capillary tubes and are uncorrected.

General method for the synthesis of 2,4,5-triaryl-1*H*-imidazoles

A mixture of sulphanilic acid (10 mol%), ammonium acetate (40 mmol), and benzil or benzoin (10 mmol) was dissolved in ethanol-water (20 ml, 1:1, v/v) and to the reaction mixture, aromatic aldehyde (12 mmol) was added. Then, the reaction mixture was heated at 80 °C till the reaction was complete (TLC). The reaction mixture was cooled to room temperature and poured on ice-water (50 ml) to get the solid precipitated. It was collected by filtration, washed with water and dried to give the corresponding 2,4,5-triaryl-1*H*-imidazoles.

All synthesized compounds were characterized with ^{1}HNMR and mass. Also the melting points recorded and compared with the corresponding literature mp and found to be matching with those. The representative analytical data for **2,4,5-triphenyl-1*H*-imidazole (3a)** Off-white solid, mp 276-277 °C (ref [17b] mp 276-277 °C), HPLC purity -99.56 %; ^{1}H NMR (400 MHz, DMSO): δ = 7.55-7.68 (m, 6H), 7.72-7.75 (m, 3H), 7.9-7.95 (m, 6H), 8.8 (bs, 1H); MS (EI, 70 eV): *m/z* = 296 $[M+H]^+$.

2-(2-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3b) Off-white solid, mp 188-189 (ref [16] mp 188 °C) °C; HPLC purity -99.18%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5-7.65 (m, 6H), 7.68-7.72 (m, 2H), 7.9-8.0 (m, 6H), 8.7 (bs, 1H); MS (EI, 70 eV): *m/z* = 330 $[M+H]^-$.

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