Use of Solid-Supported Reagents towards Synthesis of 2-Arylbenzoxazole, 3,5-Diarylisoxazole and 1,3,5-Triarylpyrazole

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ABSTRACT

Herein we report a convenient and efficient synthesis of 2-arylbenzoxazole from the Schiff’s bases of 2-aminophenol, 3,5-Diarylisoxazole from α-β-unsaturated ketoxime and 1,3,5-triarylpyrazole from 2-pyrazoline and N-Arylhydrazone by using milder, less toxic and less expensive-NBS-SiO₂, KMnO₄-Al₂O₃, PCC-SiO₂ and ACC-Al₂O₃ as solid-supported oxidizing agents at room temperature. Within the framework of Green Chemistry, the use of solid supported reagents has many advantages such as 1) they are easy to remove from reactions by filtration 2) excess reagents can be used to drive the reaction without introducing any difficulties in purification 3) such solid-supported reagents react differently, mostly more selectively, than their unbound counterparts and 4) toxic, noxious and explosive chemicals are handled more safely when contained on solid support.

Keywords: Schiff’s Bases; 3,5-Diarylisoxazoles; 2-Arylbenzoxazoles; 1,3,5-Triarylpyrazoles; Solid-Supported Reagents

1. Introduction

In the recent years heterocyclic compounds are playing important role in the synthetic organic chemistry. Among these heterocycles the bicyclic heterocycles-benzoxazoles [1-3] and five membered heterocycles pyrazoles [4,5] and isoxazoles [6-8] are known to exhibit various bioactive properties. Arylbenzoxazole possesses the important biaryl pharmacophore thus exhibiting a variety of biological and pharmacological activities such as anti-tumor [9], anti-viral [10] and many more. Isoxazoles act as intermediates in the synthesis of natural products and as building blocks for construction of new molecular systems [11]. It exhibits wide range of medicinal properties [12]. On the other hand 1,3,5-triarylpyrazole occupy an important position in agrochemicals and pharmaceutical industries due to its wide range of bioactive properties such as anti-inflammatory, anti-arrhythmic etc. [13,14].

Lot of research has been carried out and various methods have been reported towards the synthesis of 2-arylbenzoxazoles, 3,5-diarylisoxazole and 1,3,5-triarylpyrazoles in the recent years. One of such synthesis of 2-arylbenzoxazole includes oxidative cyclization of phenolic Schiff’s bases (derived from 2-aminophenols and aromatic aldehydes) using various oxidizing agents like Phl(OAc)₂ [15], Mn(OAc)₃ [16], Ba(MnO₄)₂ [17], NiO₂ [18], Pb(OAc)₄ [19] and DDQ [20]. Despite of these intensive works, the development of more effective and convenient method still remains challenging, since many of the known methods require severe reaction conditions and workup procedures. There are several routes by which 3,5-diaryl isoxazoles can be synthesized. The [5 + 0] route involving oxidative cyclization of α-β-unsaturated ketoximes using oxidizing agents like DDQ [21], MnO₂ [22], I₂/KI in NaHCO₃ [23], are some of the few known. Our method depicts use of less toxic reagent as well as good yields of product. On the other side, to carry out aromatization of 2-pyrazoline and oxidative cyclization of phenylhydrazone, limited reports are there in the literature which include reagents like Pb(OAc)₄ [24], Phl(OAc)₂ [25], Pd/C [26] and Zr(NO₃)₄ [27]. Our method stands out to be more feasible compared to literature known methods due to its versatility in variety of substrates being subjected to oxidation with good yields of the product.

In our work we report a simple, convenient and efficient procedure for the synthesis of 2-arylbenzoxazoles by oxidative cyclization of phenolic Schiff’s bases using NBS-SiO₂, synthesis of 3,5-diarylisoxazole by oxidative
cyclization of α, β-unsaturated ketoxime using ACC-Al₂O₃ and synthesis of 1,3,5-triarylpyrazoles by oxidation of 2-pyrazolines using KMnO₄-Al₂O₃, PCC-SiO₂ and oxidative cyclization of phenylhydrazones using ACC-Al₂O₃ and KMnO₄-SiO₂ as solid supported oxidizing reagents.

With our growing interest in developing greener routes towards the synthesis of these heterocycles we thought of using older and stronger oxidizing agents but adsorbed towards the synthesis of these heterocycles we thought of using older and stronger oxidizing agents but adsorbed agents are chosen to be as greener reagents due to the fact that they are mild, have good selectivity, easy to handle, easily removed after completion of reaction and reduced toxicity of the reagents.

2. Experimental Details

2.1. Typical Procedure for the Synthesis of 2-Arylbenzoxazole

All the reactions were carried out in 25 mL round bottom flask and the stirring was carried out using a magnetic stirrer. In a typical procedure the phenolic Schiff’s basse 1a (0.15 g, 0.8 mmol) was dissolved in dichloromethane (5 mL) and kept for stirring at room temperature. To this stirring mixture, NBS-Silica (0.27 g, 1.6 mmol) was added and further stirred for 30 minutes. The reaction was continuously monitored on TLC. After the completion of reaction, the mixture was filtered and the filtrate was evaporated on hot water bath. The residue that remained after evaporation was purified by column chromatography over silica gel. Yields indicated are obtained after purification.

Selected product: 2-phenyl benzoxazole (2a), white solid, melting point: 98°C - 100°C, yield = 84% \(^{1}\)H NMR (300 MHz, CDCl₃): δ 8.20 (dd, 2H), 7.75 (m, 1H), 7.48 - 7.52 (m, 4H), 7.34 - 7.38 (m, 2H). \(^{13}\)C NMR (75 MHz, CDCl₃): δ 164.0, 152.7, 143.87, 131.29, 130.89, 127.59, 126.79, 122.06, 112.6. IR (cm⁻¹): 1050, 1250, 1450, 1640, 3010.

Selected product: 2-(4’-nitrophenyl) benzoxazole (2d), pale yellow solid, melting point: 144°C, yield = 64% \(^{1}\)HNMR (300 MHz, CDCl₃): δ 8.4 (dd, 2H), 7.82 (m, 1H), 7.43 - 7.62 (m, 4H), 7.39 - 7.42 (m, 2H). \(^{13}\)CNMR (75 MHz, CDCl₃): δ 190.24, 167.0, 151.0, 141.96, 132.84, 128.43, 126.24, 125.2, 120.26, 110.6. IR (cm⁻¹): 1050, 1250, 1450, 1630, 3050.

Selected product: 2-(2’hydroxyphenyl) benzoxazole (2i), white solid, melting point: 152°C, yield = 84% \(^{1}\)HNMR (300 MHz, CDCl₃): δ 9.08 (s, 1H), 7.88 - 7.95 (m, 4H), 7.76 (s, 1H), 7.34-7.38 (m, 6H). \(^{13}\)CNMR (75 MHz, CDCl₃): δ 164.0, 152.7, 143.87, 131.29, 130.89, 127.59, 126.79, 122.06, 112.6. IR (cm⁻¹): 1050, 1250, 1450, 1630, 3400.

2.2. Typical Procedure for the Synthesis of 3,5-Diarylisoxazole

All the reactions were carried out in 25 mL round bottom flask and the stirring was carried out using a magnetic stirrer. Ketoxime 7a (1 mmol), ACC-Alumina (1 mmol) and dichloromethane were placed in a 25 mL round bottom flask. The reaction was stirred for three hours and frequently monitored using T.L.C. After completion of the reaction, the reaction mixture was filtered and filtrate obtained was then evaporated to give the product 8a.

Selected product: 3,5-diphenyl isoxazole (8a) White solid, melting point = 140°C \(^{1}\)H NMR (300 MHz, CDCl₃): -δ 6.8 (s, 1H), 7.21 - 8.05 (m, 10H). IR (cm⁻¹): 1250, 1435, 3010.

Selected product: 3-(4’-bromophenyl)-5-(4”-methoxy-phenyl) isoxazole (8c) White solid, melting point = 130°C \(^{1}\)H NMR (300 MHz, CDCl₃): -δ 5.3 (s, 3H), 6.83 (s, 1H), δ 7.34 - 7.86 (m, 10H). IR (cm⁻¹): 690, 1250, 1500, 1600, 3010.

Selected product: 3-(4’-bromophenyl)-5-phenyl isoxazole (8d) White solid, melting point = 178°C \(^{1}\)H NMR (300 MHz, CDCl₃): -δ 6.814 (s, 1H), 7.19 - 7.25 (m, 5H), 7.45 - 8.07 (m, 4H). \(^{13}\)CNMR (75 MHz, CDCl₃): 142, 135.2, 134.7, 134.09, 133.644, 133.05, 132.17, 130.157, 128, 127.646, 116.9, 95.26. IR (cm⁻¹): 685, 1250, 1510, 1600, 3010.

2.3. Typical Procedure for the Synthesis of 1,3,5-Trisubstituted Pyrazoles Using

2.3.1. KMnO₄-Alumina

All the reactions were carried out in 25 mL round bottom flask and the stirring was carried out using a magnetic stirrer. In a typical procedure the 2-pyrazoline 3a (0.15 g, 0.4 mmol) was placed in round bottom flask containing magnetic needle/pellet. To this mixture dichloromethane (5 mL) was added and kept for stirring at room temperature. To this stirring mixture, KMnO₄-Alumina (0.206 g, 0.8 mmol) was added and further stirred for four hours. The progress of the reaction was continuously monitored on TLC. After the completion of reaction, the mixture was filtered and the filtrate was evaporated on hot water bath. After evaporation, a pale yellow solid pyrazole is obtained which was purified by recrystallization using ethanol as solvent.

Selected product: 1,3,5-triphenylpyrazole (4a), pale yellow solid, melting point: 144°C, yield = 66% \(^{1}\)H NMR (300 MHz, CDCl₃): δ 6.8 (s, 1H), 7.21 - 7.45 (m, 13H), 7.92 (d, 2H) IR (cm⁻¹): 1495, 1500, 1600, 3010.

2.3.2. PCC-SiO₂

All the reactions were carried out in 25 mL round bottom flask and the stirring was carried out using a magnetic stirrer. In a typical procedure the 2-pyrazoline 5b (0.15 g, 0.8 mmol) was placed in round bottom flask containing magnetic stirrer. In a typical procedure the pyrazoline 5b (0.15 g, 0.8 mmol) was placed in round bottom flask containing magnetic stirrer. Ketoxime 7b (1 mmol), ACC-Alumina (1 mmol) and dichloromethane were placed in a 25 mL round bottom flask. The reaction was stirred for three hours and frequently monitored using T.L.C. After completion of the reaction, the reaction mixture was filtered and filtrate obtained was then evaporated to give the product 8d.
0.4 mmol) was placed in round bottom flask containing magnetic needle/pellet. To this mixture dichloromethane (5 mL) was added and kept for stirring at room temperature. To this stirring mixture, PCC-Silica (0.546 g, 2 mmol) was added and further stirred for five hours. The progress of the reaction was continuously monitored on TLC. After the completion of reaction, the mixture was filtered and the filtrate was evaporated on hot water bath. After evaporation, a pale yellow solid pyrazole is obtained which was purified by recrystallization using ethanol as solvent.

Selected product: 5-(4’-chlorophenyl)-1,3-diphenyl pyrazole (6b), pale yellow solid, melting point: 116°C, yield = 51% 1H NMR (300 MHz, CDCl3): δ 6.83 (s, 1H), 7.20 - 7.29 (m, 5H), 7.31 - 7.42 (m, 5H), 7.92 (d, 2H), 7.45 (d, 2H) IR (cm⁻¹): 670, 1490, 1600, 3015.

2.3.3. KMnO₄-Silica
All the reactions were carried out in 25 mL round bottom flask and refluxing was carried out using a heating mantle. In a typical procedure the parent phenylhydrazone 9a (0.15 g, 0.33 mmol) was placed in round bottom flask. To this mixture dichloromethane (5 mL) was added and kept for stirring at room temperature. To this stirring mixture, KMnO₄-Silica (0.546 g, 0.33 mmol) was added and further refluxed for three hours. The progress of the reaction was continuously monitored on TLC. After the completion of reaction, the mixture was filtered and the filtrate was evaporated on hot water bath. After evaporation, a pale yellow solid pyrazole is obtained which was purified by recrystallization using ethanol as solvent.

Selected product: 5-(4’-chlorophenyl)-1,3-diphenyl pyrazole (6b), pale yellow solid, melting point: 116°C, yield = 63% 1H NMR (300 MHz, CDCl3): δ 6.7 (s, 1H), 7.1 - 7.4 (m, 5H), 7.76 - 7.83 (m, 4H), 7.88 (d, 1H), 8.75 (d, 1H), 9.056 (d, 1H).

13C NMR (75 MHz, CDCl3): δ 116, 117, 126, 127, 128.3, 128.4, 128.7, 129.05, 129.11, 129.45, 129.46, 129.53, 129.6, 129.91, 130.0, 130.19, 130.39, 132.61, 137.469, 141.3, 156.1, 157.5.

Selected product:

5-(p-methoxyphenyl)-3-(p-nitrophenyl)-1-(2’, 4’-dinitrophenyl) pyrazole (12b), yellow solid, melting point: 166°C, yield = 73% IR (cm⁻¹): 1248, 1290, 1490, 1600, 3050 1H NMR (300 MHz, CDCl3): δ 3.88 (s, 3H), 6.90 (s, 1H), 7.25 - 7.44 (m, 4H), 7.78 (d, 2H), 7.35 (d, 2H) 7.79 (d, 2H), 8.74 (d, 1H).

Selected product:

5-(p-chlorophenyl)-3-(p-methoxyphenyl)-1-(2’, 4’-dinitrophenyl) pyrazole (12c), yellow solid, melting point: 132°C; yield = 50% IR (cm⁻¹): 1255, 1280, 1520, 1620, 3070 1H NMR (300 MHz, CDCl3): δ 3.85 (s, 3H), 6.87 (s, 1H), 7.22 - 7.48 (m, 4H), 7.70 (d, 2H), 7.40 (d, 2H) 7.82 (d, 2H), 8.80 (d, 1H).

3. Results and Discussion
Initially, we prepared nine phenolic Schiff’s bases by reacting aromatic aldehydes with 2-aminophenol. Once the Schiff’s bases were prepared, we carried out oxidative cyclization on it. Here the parent Schiff’s base, prepared from benzaldehyde and 2-aminophenol, was dissolved in dichloromethane to which NBS-silica was added and kept for stirring at room temperature for 30 minutes. After that the reaction mixture was filtered so as to remove the solid support. The filtrate was concentrated and purified using column chromatography. The product, 2-phenyl benzoazoxazole was obtained in 84% yield after recrystallization. To check the feasibility of this reaction the remaining Schiff’s bases (those prepared earlier) were also tried for similar oxidative cyclization using NBS-silica as the oxidizing agent. In all nine 2-arylbenzoazoxazoles were prepared in moderate-good yields (60% - 84%) after chromatographic separation and purification (Scheme 1, Table 1).

Next task was to synthesize 1,3,5-trisubstituted pyrazoles from the corresponding 2-pyrazolines. In this case the parent pyrazoline, which was synthesized from phenyl hydrazine and chalcone was dissolved in dichloromethane and to this solution KMnO₄-Alumina was added. The reaction mixture was stirred for four hours at room temperature. After the completion of reaction, the mixture was filtered and the filtrate was evaporated to give a pale yellow solid pyrazole as the product which was purified by recrystallization using ethanol. In all three 1,3,5-trisubstituted pyrazoles were prepared in good yields.
after purification (Scheme 2, Table 2).

We also used another reagent i.e. PCC-Silica for the oxidation of 2-pyrazolines to the corresponding 1,3,5-trisubstituted pyrazoles. Here the parent 2-pyrazoline was dissolved in dichloromethane and then subjected to oxidation by adding PCC-Silica. The reaction mixture was stirred for five to six hours at room temperature. After the completion of reaction, the mixture was filtered and then the filtrate was evaporated to give a pale yellow solid pyrazole as the product which was purified by recrystallization using ethanol. In all three 1,3,5-trisubstituted pyrazoles were prepared in good yields after purification (Scheme 3, Table 3).

In addition, we also prepared 3, 5-diarylisoxazole from the corresponding α, β-unsaturated ketoxime. The α, β-unsaturated ketoxime was initially prepared by reacting α, β-unsaturated chalcones with hydroxylamine hydrochloride under weakly basic conditions. Once the α, β-unsaturated ketoxime were prepared, we carried out oxidative cyclization on it. Here the parent α, β-unsaturated ketoxime was dissolved in dichloromethane to which ACC-Alumina was added and kept for stirring at room temperature for three hours. After that the reaction mixture was filtered so as to remove the solid support. The filtrate was concentrated and purified by recrystallization using absolute ethanol as the solvent. To check the feasibility of this reaction the remaining α, β-unsaturated ketoxime were also tried for similar oxidative cyclization using ACC-Alumina as the oxidizing agent. In all five 3, 5-diarylisoxazole were prepared in moderate-good yields after purification (Scheme 4, Table 4).

Since we were also successful in synthesizing 1,3,5-
trisubstituted pyrazoles from 2-pyrazolines, we thought of preparing 1,3,5-trisubstituted pyrazoles from the corresponding N-Arylhydrazine and 2,4-dinitrophenylhydrazone via oxidative cyclization. For which we used KMnO4-silica and ACC-alumina as the oxidizing agents. Here the parent phenyl hydrazone was initially synthesized from phenyl hydrazine and chalcone under acidic conditions. This phenyl hydrazone was dissolved in dichloromethane and then subjected to oxidative cyclization by adding KMnO4-silica. The reaction mixture was refluxed for three hours. After the completion of reaction, the mixture was filtered and the filtrate was evaporated to give a pale yellow solid pyrazole as the product which was purified by recrystallization. In all three 1,3,5-trisubstituted pyrazoles were prepared in good yields after purification (Scheme 5, Table 5).

Similarly the 2,4-dinitrophenylhydrazone was dissolved in dichloromethane and then subjected to oxidative cyclization by adding ACC-alumina. The reaction mixture was refluxed for three hours. After the completion of reaction, the mixture was filtered and the filtrate was evaporated to give a pale yellow solid pyrazole as the product which was purified by recrystallization. In all three 1,3,5-trisubstituted pyrazoles were prepared in good yields after purification (Scheme 6, Table 6).

4. Conclusion

In conclusion, we have been successful in developing a convenient, efficient and greener method for the synthesis of 2-arylbenzoxazoles from phenolic Schiff’s bases, 3,5-diarylisoxazole from α, β-unsaturated ketones and 1,3,5-trisubstituted pyrazoles from the pyrazolines and N-Arylhydrazones respectively. All the reactions were carried out at room temperature and the conditions used were quite mild. The product yields The products are obtained in moderate-good yield, which is compatible with literature known methods and moreover our methodology is eco-friendly. This methodology also shows greater versatility of using solid-supported reagents towards synthesis of variety of heterocycles. Use of solid supported reagents in our reaction has reduced the toxicity of the reagent which makes it much safer and easier to handle.

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REFERENCES


