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Acid Catalyzed Direct-Amidation–Dehydrocyclization of 2-Hydroxy-acetophenones to Benzoxazoles by a One-Pot Sustainable Synthesis

Elia Rancan · Fabio Aricò · Giuseppe Quartarone · Lucio Ronchin · Andrea Vavasori

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Abstract A series of 2-methyl-benzoxazoles have been synthesized starting from 2-hydroxy-acetophenones via a one-pot three steps reaction. Hydroxylamonium salt has been used as amidation agent. The reaction occurs with different anions, but the best results is achieved with hydroxylamonium hydrchloride. Despite the number of consecutive stages, the reaction is highly selective. Mild reaction conditions and various solvents can be used, but trifluoroacetic acid is the preferred. Almost, complete recovery of the trifluoroacetic acid can be achieved by vacuum distillation. The role of trifluoroacetic acid, as well as, of the hydroxylamonium salt suggests a cooperative effect leading to high selective formation of 2-methyl-benzoxazoles.

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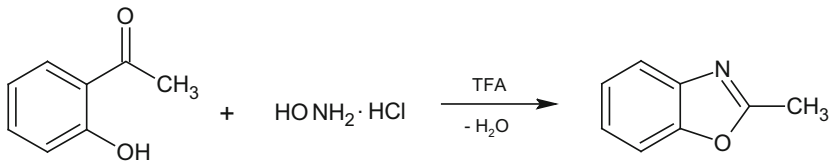

Keywords Benzoxazoles · Direct-amidation–dehydrocyclization · Trifluoroacetic acid · Acid catalysis

1 Introduction

In the field of fine chemicals, the development of new and efficient synthetic strategies with higher atom economy has been continuously pursued by industrial researchers as it represents a great chance to develop sustainable processes from both economical and environmental point of view [1]. The recent trends for greener strategy are mainly based on converting multi stages synthesis in one-pot process by reducing plant operations, as well as, formation of

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E. Rancan · G. Quartarone · L. Ronchin (✉) · A. Vavasori
Department of Molecular Science and Nanosystems, Ca' Foscari University, 2137 Dorsoduro, 30123 Venice, Italy
e-mail: ronchin@unive.it

E. Rancan · F. Aricò · G. Quartarone · L. Ronchin · A. Vavasori
Green Chemistry Group, 2137 Dorsoduro, 30123 Venice, Italy

F. Aricò
Department of Environmental Science, Informatics and Statistics, Ca' Foscari University, 2137 Dorsoduro, 30123 Venice, Italy

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unwanted by-products or wastes, being the latter a typical consequence of the multi-workup operations [2].

Heterocycles such as indoles and benzoxazoles are interesting intermediates for a wide variety of products ranging from herbicides, optical brighteners, to drugs and pharmaceutical, corrosion inhibitors, intermediates in general [3, 4].

As an example, in the last 10 years several investigations have been reported on benzoxazole-based chemotherapics [5–8]. In particular, medicinal chemistry applications of benzoxazoles include anticancer agent [9] and drugs for Alzheimer's disease [10]. Studies conducted on this class of heterocycles indicate that their wide range of biological activities derive from oxazoles moiety [11].

Typically oxazoles are synthesized by multistep reaction involving as starting reagents *o*-aminophenols, usually obtained by nitration of phenols and successive reduction of the corresponding nitro-compound [12]. The synthesis of oxazole via aminophenols is well known and it involves acid or base catalyzed condensation reaction with aldehydes, nitriles, BrCN, ClCOAr and in general with other carbonyl electrophiles [13, 14]. Other synthetic paths, which use as reagents 2-Br-anilines and/or di-halogen-aryl compounds, have been also reported, although they still involve multistep procedures [13].

Therefore, a versatile pool of starting materials is available for a large range of benzoxazole products, however, multistep approaches and the use of expensive building blocks limit the sustainability of the synthesis from both environmental and economic point of view [13].

In this context we report for the first time a new synthetic strategy to benzoxazoles starting from 2-hydroxyacetophenone, a cheap reagent since large amounts of this ketones are available from Fries rearrangement of aril acetates, a widely employed reaction in fine chemistry [15–17].

In fact, it is well known, that the selectivity of Fries rearrangement of phenyl acetate to 4-hydroxyacetophenone, which is the key intermediate in the acetaminophen manufacture via Hoechst–Celanese process, reaches about 90–94 % of selectivity to the 4-position [18]. The main by-product formed is the isomer 2-hydroxyacetophenone, which has limited application as chelating agent for metal recovery or as intermediate in fine chemistry [19].

In Fries rearrangement, though solvent and catalyst play important roles, the control of the *ortho*/*para* ratio is mainly determined by temperature that is at high temperature (165 °C) the *ortho* isomer is favored, while at low temperature (25 °C) the *para* is the preferred one. In any case, the selectivity towards one of the two isomers is never complete, at most 90–95 % selectivity can be reached [16–18]. For this reason, in order to improve the efficiency and the sustainability of the Hoechst–Celanese process, it is crucial to find an economically convenient use of 2-hydroxyacetophenone being a byproduct obtained in non negligible amount [16–19].

It is noteworthy that an electrophilic attack to the phenyl ring of 2-hydroxyacetophenone is favored due to the activation of the hydroxyl group, thus allowing a wide range of products to be used as intermediates for fine and/or medicinal chemistry [20].

Among the products that can be obtained from 2-hydroxyaril aldehyde and ketones, benzoxazoles are the ones that can be synthesized in high yield from the corresponding aldoximes and ketoximes via a two step reaction: (1) Beckmann rearrangement, (2) dehydration-cyclization (see Scheme 1) [3, 21, 22].

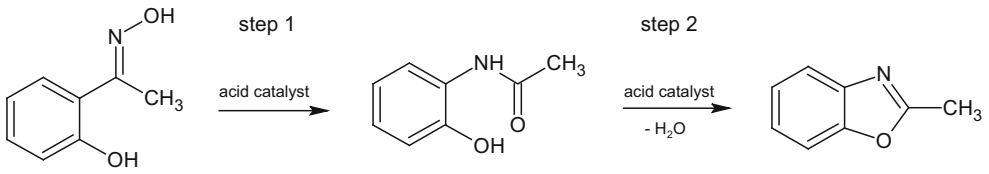
We have already reported Beckmann rearrangement of various oximes by using TFA as organocatalyst focusing on its applications for the high yielding synthesis of amides [23–26]. Recently, also Luo and coworkers have studied the reactivity of TFA in the Beckmann rearrangement of cyclohexanone oxime obtaining similar results [27–30]. In particular, in our case study, caprolactam, acetanilide and other amides were synthesized from the corresponding ketones in neat by using TFA as solvent–catalyst and hydroxylamine hydrochloride [30]. The reaction proceeds in one-pot by oximation and Beckmann rearrangement of the ketones to the corresponding amides by following a two-stages mechanism whose kinetics is influenced by ketones structure [29, 30]. Furthermore, recently, we investigated the reaction between ketones and $NH_2OH{\cdot}HCl$ in the absence of acid catalyst, where we demonstrated an autocatalytic effect of the HCl released after the nucleophilic attack of NH_2OH to carbonyl group of ketones [30].

In these reactions the role of the solvent is of paramount importance to achieve good yield and selectivity, as well as that of temperature. As a matter of fact, the balance of these reaction parameters allows high amide yield.

On the light of these findings, we postulated that benzoxazole could be synthesized using 2-hydroxyacetophenones as building block via Beckmann rearrangement of the corresponding oximes.

So far, only one example of the one-step synthesis of benzoxazole via oximation-Beckmann rearrangement-dehydrocyclization of 2-hydroxyaryl ketones has been reported. However, this reaction was carried out in the presence of mineral acid and by microwave irradiation, being this procedure neither industrially convenient nor environmentally benign [31].

Therefore, in this work we report on a new procedure for the catalytic synthesis of benzoxazoles employing 2-hydroxyacetophenones as building block for heterocycles of industrial interest by using hydroxylamonium salts as amidation agent. The synthesis proceeds via a catalytic direct-amidation–dehydrocyclization, which gives benzoxazoles



Scheme 1 2-Methyl benzoxazole synthesis from 2-hydroxy-acetophenone oxime

in high yields. In addition, the influence of the solvents and the role of the acidity of the system on benzoxazoles selectivity have been investigated.

2 Experimental

All the solvents and products were employed as received without further purification. 2-Hydroxyacetophenone ≥98 %, 4-methyl-2-hydroxyacetophenone ≥95 %, 5-methyl-2-hydroxyacetophenone ≥98 %, 5-Br-2-hydroxyacetophenone 98 %, 5-NO_2-2-hydroxyacetophenone 98 %, TFA 99 %, hydroxylamine hydrochloride 99 %, hydroxylamine Sulfate 99 %, hydroxylamine phosphate 99 % and acetonitrile were all Aldrich products. Deuterated chloroform and deuterated DMSO-d6 were EurisoTop products.

All the reactions were carried out in a well stirred pressurized glass reactor thermostated at temperatures comprised between 70 and 170 °C containing weighed samples of the solvent and reagents typically 10 mmol of the selected ketone, 30 mmol of $NH_2OH{\cdot}HCl$ and 200 mmol of solvent (TFA, CH_3COOH, CH_3CN).

Reaction products were analyzed by gas chromatograph (GC), gas chromatograph coupled with mass spectroscopy (GC–MS) and by high performance liquid chromatography (HPLC). The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 25 °C, using as internal standard to tetramethylsilane.

Products with sufficient purity for obtaining precise NMR spectra were obtained from the mixture of reaction by the following procedure: (i) vacuum distillation of TFA (at 40 °C and 250 Pa of pressure in a rotary evaporator); (ii) the oily phase was washed with water and extracted with dichloromethane; (iii) the extracted was dried with anhydrous sodium sulfate and the solvent eliminated in a rotary evaporator; (iv) the solid was purified by column chromatography employing hexane/ethyl acetate 9:1 as elution mixture and the solvent is eliminated in rotary evaporator. The solid is weighted and analyzed by NMR (isolated yield and NMR spectra in supplementary materials).

2-Methyl-1,3-benzoxazole had *m/z* GC–MS calc. for C_8H_7NO [M^+] 133.05, found 133.1; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.67 (s, 3H), 7.26–7.32 (m, 2H), 7.47–7.49 (d, 1H), 7.66–7.69 (d, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 14.47, 110.63, 119.23, 124.79, 125.16, 140.15, 150.88, 164.65.

2,5-Dimethyl-1,3-benzoxazole had *m/z* GC–MS calc. for C_9H_9NO [M^+] 147.07, found 147.1; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 2.63 (s, 3H), 7.08–7.11 (d, 1H), 7.31–7.33 (d, 1H), 7.45 (bs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 14.44, 21.55, 109.96, 119.10, 126.17, 134.68, 140.29, 149.11, 164.66.

2,6-Dimethyl-1,3-benzoxazole had *m/z* GC–MS calc. for C_9H_9NO [M^+] 147.07, found 147.1; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.46 (s, 3H), 2.67 (s, 3H), 7.13–7.15 (d, 1H), 7.29 (bs, 1H), 7.55–7.57 (d, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 14.26, 21.83, 110.90, 118.28, 126.27, 135.98, 136.91, 150.99, 164.41.

5-Bromo-2-methyl-1,3-benzoxazole had *m/z* GC–MS calc. for C_8H_6BrNO [M^+] 210.96, found 211.0; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.63 (s, 3H), 7.26–7.32 (d, 1H), 7.38–7.41 (d, 1H), 7.78 (bs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 14.70, 111.71, 117.20, 122.56, 127.83, 142.88, 150.08, 165.47.

For more experimental details see supplementary materials.

3 Results and Discussion

3.1 Synthesis of 2-methyl-benzoxazole: influence of operating conditions

The synthesis of 2-methyl-benzoxazole from 2-hydroxy acetophenone by catalytic direct-amidation–dehydrocyclization occurs in high yield by using TFA as solvent-acid catalyst at 140 °C at autogenous TFA pressure.

Table 1 shows the results of the influence of the TFA on conversion and selectivity towards 2-methyl-benzoxazole. Increasing the amount of TFA from 50 to 300 mmol, the conversion of 2-hydroxy acetophenone was in any case almost quantitative, i.e. 90–99 %. On the contrary the selectivity to 2-methyl-benzoxazole reach 97 % at 200 mmol of TFA in the presence of 30 mmol of NH_2-$OH{\cdot}HCl$ and no further increase in the selectivity is observed even at higher concentration of TFA.

Table 1 Influence of the TFA amount on the direct-amidation–dehydrocyclization of 2-hydroxyacetophenone

TFA (mmol)	$NH_2OH{\cdot}HCl$ (mmol)	Conversion (%)	Selectivity (%)			Notes
			2MB	2HAA	Other	
50	30	98	87	1	12	Pale orange
100	30	99	89	1	10	Pale orange
200	10	90	92	2	6	Pale yellow
200	20	95	95	1	4	Pale yellow
200	30	99	97	1	2	Pale yellow
200	40	99	96	1	3	Yellow
300	30	99	97	1	2	Pale yellow

Run conditions: T 140 °C, substrate 10 mmol, time of reaction 1 h

2MB 2-methylbenzoxazole, *2HAA* 2-hydroxyacetanilide

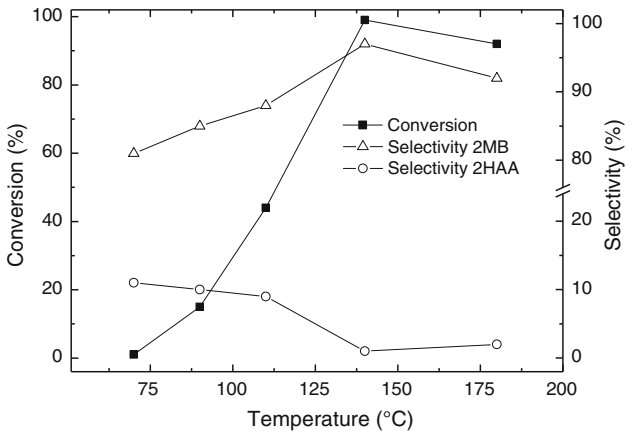


Fig. 1 Influence of the temperature on the direct-amidation–dehydrocyclization of 2-hydroxyacetophenone. Run conditions: substrate 10 mmol, $NH_2OH{\cdot}HCl$ 30 mmol, TFA 200 mmol

Figure 1 shows the influence of temperature on the direct-amidation–dehydrocyclization, substrate conversion is practically quantitative at 140 °C, while at 170 °C a small decrease in conversion and selectivity is observed, most probably due to hydroxylamine decomposition [32, 33]. In addition, the product obtained at the highest temperature is dark, and a black precipitate is observed suggesting formation of pitch by thermal and acid catalyzed side reactions, such as condensation and oxidation reactions [23–25].

Interestingly, when the reaction was performed at lower temperatures (namely 70, 90 and 110 °C) the selectivity towards 2-hydroxyacetanilide increases. This suggests that the reaction proceeds by formation of 2-hydroxyacetanilide, which derives likely from Beckmann rearrangement of the 2-hydroxyacetophenone oxime, then, the dehydrocyclization of 2-hydroxyacetanilide gives finally the benzoxazole. In fact, this behavior is easily explained, by considering that the increase of temperature favors the dehydrocyclization for entropic reasons. It is noteworthy that 2-hydroxyacetophenone oxime has never been observed in the presence of TFA in the direct-amidation–dehydrocyclization of 2-hydroxyacetophenone, but it has been detected if different solvent and/or acetophenones have been used (see Sect. 3.3).

Table 2 shows the reactivity of various hydroxylamonium salt in the direct-amidation–dehydrocyclization of 2-hydroxyacetophenone. A modest variation of conversion and selectivity towards 2MB has been observed when the amount of $NH_2OH{\cdot}HCl$ was increased from 10 to 60 mmol in agreement the results reported in Table 1.

$NH_2OH{\cdot}HCl$ gives 2-methylbenzoxazole in almost quantitative yields at 140 °C, while, $NH_2OH.H_2SO_4$ gives high conversion and good selectivity at 90 °C, but very poor selectivity to 2-methylbenzoxazole at 140 °C. Phosphate salt results, on the other hand, the less efficient hydroxylamonium salt.

The reason of this behavior is not clear, however, it is evident that the type of anion drives the selectivity to 2-methylbenzoxazole. A possible explanation to these results could be ascribed to the stability of the hydroxylamine employed, whose decomposition may promote side reactions, which determines a noticeable decline of the selectivity to 2-methylbenzoxazole, too [32, 33]. In addition, the influence of the steric hindrance of the anion cannot be ruled out, thus explaining the specific reactivity of each hydroxylamonium salt.

3.2 Influence of the Substituent on the Synthesis of Benzoxazoles

The general application of the method was then tested by using different substituted 2-hydroxycetophenones. The results are reported in Table 4. In order to compare the different reactivity of each substrate we carried out the experiments at 90 °C (16 h reaction time) or at 140 °C (1 h reaction time). At 140 °C we observed quantitative conversions with selectivities ranging from 93 to 98 % except for 5-nitro-2-hydroxyacetophenone, which reach a modest 69 %. At 90 °C, conversions were in the range of 62–75 % with selectivities to the corresponding benzoxazole raging from 90 to 96 % for all the substrates except for the 5-nitro-2-hydroxyacetophenone, which shows a conversion

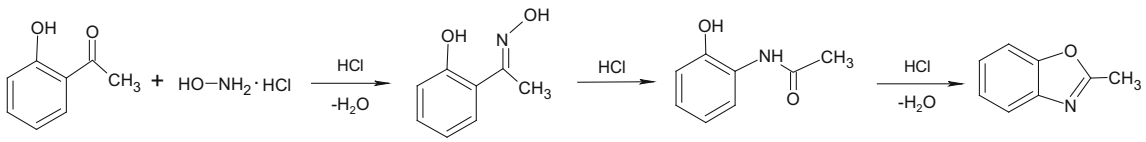
Table 2 Influence of the type of hydroxylamonium salt on the direct-amidation–dehydrocyclization of 2-hydroxyacetophenone

$NH_2OH{\cdot}AH$	$NH_2OH{\cdot}AH$[a] (mmol)	Time (h)	T (°C)	Conversion (%)	Selectivity (%)			Notes
					2MB	2HAA	Other	
AH type								
HCl	10	16	90	62	90	7	3	Pale yellow
HCl	30	16	90	64	91	6	3	Pale yellow
HCl	60	16	90	66	91	6	3	Pale yellow
HCl	30	1	140	99	97	1	2	Pale yellow
H_2SO_4	30	16	90	96	95	/	5	Orange-brown
H_3PO_4	30	16	90	95	68	/	32	Brown
H_2SO_4	30	1	140	99	68	/	32	Brown
H_3PO_4	30	1	140	99	15	/	85	Dark brown

Run condition: reaction time 1 h, 2HAP 10 mmol, TFA 200 mmol

2MB 2-methylbenzoxazole, *2HAA* 2-hydroxyacetanilide

[a] AH = HCl or H_2SO_4 or H_3PO_4



Scheme 2 Steps observed in the direct-amidation–dehydrocyclization of 2-hydroxyacetophenone

of 95 % with a selectivity to benzoxazole of only 62 %. These results suggest a strong effect of the nitro-group on the selectivity of the reaction, although the reason of this behavior is not evident. As a matter of fact, the electro-withdrawing effect of the nitro-group might promote side reactions, thus decreasing the selectivity to the respective benzoxazole. Furthermore, there is an evident influence of the methyl group position on the aromatic ring as demonstrated by the higher conversion of 5-methyl-2-hydroxyacetophenone (similar reactivity of 5-bromo-2-hydroxyacetophenone) compared to 4-methyl-2-hydroxyacetophenone, the latter is comparable with the unsubstituted 2-hydroxyacetophenone. In any case, results collected showed that this procedure is efficient for the synthesis of all the substituted benzoxazoles confirming its potential application for the preparation of fine chemicals intermediates.

3.3 Influence of the Solvent on the Synthesis of Benzoxazoles

Solvent is of paramount importance in the synthesis of organic compounds; in catalytic reactions it plays an important role by influencing both activity and selectivity of the catalyst [34–36]. Besides in this kind of reaction, in which is not clear what is the catalytic medium, the role of the solvent is even more important [23–30]. In fact, the catalysis may derive from the solvent (e.g. TFA) or from a self–catalysis induced by hydroxylamine salt, which releases a mol. eq. of acid after nucleophilic attack to the carbonyl (e.g. HCl, H_2SO_4 and H_3PO_4), or even more likely by the combined effect of the two phenomena.

Table 4 reports on the influence of the solvent combined with other reaction parameters. Comparing the reactivity of different substrates in the presence of various solvents, it is evident that the reaction proceeds via a multistep path (Scheme 2).

In any case, as reported in previous sections, in order to achieve high substrate conversion and elevated selectivity to benzoxazoles, it is mandatory to employ TFA as solvent–catalyst (see Table 3 in Sect. 3.2). The use of different solvents such as CH_3CN or CH_3COOH, shows much lower selectivity to benzoxazoles (see entries 5, 11, 15, 19 in CH_3CN, 9, 13, 17, 21 in CH_3COOH for 2-hydroxyacetophenone, 5-methyl-2-hydroxyacetophenone, 6-methyl-2-hydroxyacetophenone and 5-bromo-2-hydroxyacetophenone, respectively). 5-Nitro-2-hydroxyacetophenone gives mainly side reactions and lower selectivity to benzoxazole, except when CH_3CN is used as the solvent at 90 °C (entry 22), in which a selectivity of 94 % is achieved although with a modest conversion (29 %). Such result suggests, however, that there are large possibilities of improvement on the

Table 3 Influence of the substituent on the synthesis of benzoxazoles starting from substituted 2-hydroxyacetophenones

Substrate	Temperature (°C)	Time of reaction (h)	Conversion (%)	Selectivity (%)			Notes
				RMB	RHAA	Other	
2HAP	90	16	64	91	6	3	Dark orange
2HAP	140	1	99	97	1	2	Dark orange
5M2HAP	90	16	78	96	2	2	Light green
5M2HAP	140	1	99	98	/	2	Dark orange
4M2HAP	90	16	62	96	1	3	Dark red
4M2HAP	140	1	99	93	1	6	Dark red brown
5Br2HAP	90	16	75	96	1	3	Dark red
5Br2HAP	140	1	99	95	/	5	Dark red brown
5N2HAP	90	16	95	62	5	33	Red
5N2HAP	140	1	99	69	/	31[a]	Black

Run conditions: substrate 10 mmol, $NH_2OH{\cdot}HCl$ 30 mmol, TFA 200 mmol, time of reaction 16 h

RMB benzoxazoles, *RHAA* amides

[a] Mainly complex condensation products are observed by GC–MS

Table 4 Influence of the solvent on the synthesis of benzoxazoles starting from substituted 2-hydroxyacetophenones

Entry	Substrate	Solvent	Temperature (°C)	Time of reaction (h)	Conversion (%)	Selectivity (%)			
						RMB	RHAPO	RHAA	other
1	2HAP	CH_3CN	70	16	14	10	/	87	3
2	2HAP	CH_3CN	90	16	48	79	11	8	2
3	2HAP	CH_3CN[a]	90	16	98	/	98	/	2
4	2HAP	CH_3CN[b]	90	16	97	97	/	/	3
5	2HAP	CH_3CN	140	1	87	74	12	9	5
6	2HAP	CH_3CN[c]	140	1	15	95	1	/	4
7	2HAP	CH_3CN[d]	140	1	7	1	98	/	1
8	2HAP	CH_3COOH	90	16	87	90	8	1	1
9	2HAP	CH_3COOH	140	1	99	1	\	\	99
10	5M2HAP	CH_3CN	90	16	54	72	15	12	
11	5M2HAP	CH_3CN	140	1	90	84	5	9	
12	5M2HAP	CH_3COOH	90	16	87	91	2	6	1
13	5M2HAP	CH_3COOH	140	1	99	50		40	10
14	4M2HAP	CH_3CN	90	16	26	74	13	11	
15	4M2HAP	CH_3CN	140	1	79	69	10	19	
16	4M2HAP	CH_3COOH	90	16	56	90	2	5	3
17	4M2HAP	CH_3COOH	140	1	99	70	/	30	
18	5B2HAP	CH_3CN	90	16	59	82	5	7	6
19	5B2HAP	CH_3CN	140	1	85	59	25	5	11
20	5B2HAP	CH_3COOH	90	16	61	87	10	1	2
21	5B2HAP	CH_3COOH	140	1	99	80	2	8	20
22	5N2HAP	CH_3CN	90	16	29	94	/	1	5
23	5N2HAP	CH_3CN	140	1	97	5	/	/	95[e]
24	5N2HAP	CH_3COOH	90	16	59	1	64	25	10
25	5N2HAP	CH_3COOH	140	1	99	1	/	/	99[e]

Run conditions: substrate 10 mmol, $NH_2OH{\cdot}HCl$ 30 mmol, solvent 200 mmol

RMB benzoxazoles, *RHAPO* oximes, *RHAA* amides

[a] In the presence of 3 equivalents of pyridine

[b] In the presence of 3 equivalents of CH_3SO_3H

[c] Hydroxylamine sulfate

[d] Hydroxylamine phosphate

[e] Final solution is dark-black and mainly complex condensation products are observed by GC–MS

overall yield for many substrates by controlling reaction conditions, thus extending the synthesis capabilities of the method. This behavior clearly indicates the influence of the solvent on the reaction, but, it also suggests that the reaction may follow an autocatalytic path due to the presence of the hydroxylamonium salt, which release HCl after the

nucleophilic attack of NH_2OH to the carbonyl, as already pointed out in a our previous paper [30]. This hypothesis is confirmed by the reactivity of the 2-hydroxyacetophenone in CH_3CN as a solvent in the presence of pyridine (entry 3), where only the 2-hydroxyxacetophenone oxime is selectively obtained. The evidence that an autocatalytic path concurs in the reaction is in agreement with the different reactivity of three hydroxylamonium salt in CH_3CN as a solvent (see entries 5–7). In fact, as already observed in Table 3 in TFA, $NH_2OH{\cdot}HCl$ gives the best results and both hydroxylamonium sulfate and phosphate give lower conversion, and in the case of phosphate salt shows negligible selectivity in the 2-methylbenzoxazole. The specific reactivity of each anion suggests its active function as self–catalyst. In additions, it is not clear the role of TFA as active solvent in the amidation reaction, since TFA may acts as Brønsted acid catalyst, similarly to CH_3SO_3H in CH_3CN (entry 4), or as an organocatalyst as already demonstrated in the Beckmann rearrangement of several ketoximes [23–30]. However, the study of the mechanism of reaction, the kinetics, and the specific role of hydroxylamonium salts and solvents are items beyond the scope of the present work.

The influence of solvent, on the reactivity of 4- and 5-methyl substituted hydroxyacetophenones, suggests a trend analogous of that observed in Table 4 (compare entries: 2, 8 for 2-hydroxyacetophenone, 10, 12 for 5-methyl-2-hydroxyacetophenone and 14, 16 for 6-methyl-2-hydroxyacetophenone). Similar activation effect is also observed for 5-bromo-2-hydroxyacetophenone (see entries 18, 20).

4 Conclusions

In this work we report on the direct-amidation–dehydrocyclization of ketones for the synthesis of benzoxazoles. This procedure for benzoxazoles synthesis is simple and gives benzoxazoles in high yield via a cascade reaction, thus allowing a sustainable and environmentally benign process for the production of an interesting building block useful in medicinal and fine chemistry.

Several reaction parameters have been investigated, i.e., amount of TFA, type of hydroxylamonium salt and reaction media.

The optimum conditions encompassed 30 mmol of TFA (Table 1) and $NH_2OH{\cdot}HCl$ as reagent. $NH_2OH.H_2SO_4$ showed also good conversion and selectivity, but it required longer reaction time (17 h), whereas $NH_2OH.H_3PO_3$ gave MB only in traces. The so found best reaction condition have then been tested on different substituted 2-hydroxy-acetophenones in order to investigate general applicability of the synthetic methodology. The effect of methyl (in position 4- or 5-), bromo (in position 5-) and nitro (5- position) moieties was taken into account. In all cases it was observed the quantitative conversion of the substrates with good selectivity (93–98 %) except for 5N2HAP (69 %). This results suggest an effect of the nitro-group on the selectivity possibly due to its electro-withdrawing effect which probably promotes unwanted side reactions.

Finally tests conducted employing different solvents indicated that the reaction can be efficiently carried out in several solvents such as CH_3COOH and CH_3CN.

From a mechanicistic point of view, the direct-amidation–dehydrocyclization reaction herein described is an example of a self-acid catalysis originated from the nucleophilic attack of the hydroxylamonium salt to the carbonyl group of the ketone, which release an acid (e.g. HCl). The reaction is promoted by TFA, which acts as active solvent likely acting not only as catalyst.

The reaction appears to follow the one-pot oximation-Beckmann rearrangement-dehydrocyclization reaction path; a three-stages process whose steps are well known reactions. In this way, the control of the overall process for industrial application would be easy and of simple implementation.

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