Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(8):97-101
(http://derpharmachemica.com/archive.html)

NaH_2PO_4 catalyzed a three-component 4-arylidene-3-methylisoxazol-5(4*H*)-ones synthesis in solvent-free conditions

Imène Amine Khodja, Raouf Boulcina, Taous Boumoud, Boudjemaa Boumoud and Abdelmadjid Debache*

Laboratoire de synthèse de molécules d'intérêts biologiques, Université de Constantine, Algérie

---

ABSTRACT

Some 4-arylidene-3-methylisoxazol-5(4H)-ones were synthesized via a one-pot three-component reaction of ethyl acetoacetate with hydroxylamine hydrochloride and various aromatic aldehydes using sodium dihydrogen sulfate as catalyst in a solvent-free conditions in high yields and short reaction time.

Keywords: sodium dihydrogen sulfate, three-component reaction, isoxazol-5(4*H*)-ones, solvent-free medium.

INTRODUCTION

Heterocycles containing isoxazol moety show several biological activities such as antitumor [1], antimicrobial [2], Antioxidant [3], anti-inflammatory [4], antiviral [5], antituberculosis [6], fungicial [7], nematicidal [8], antimycobacterial [9], anticancer [10], analgesic [11]. They are also COX-2 (cyclooxygenase-2) [12] and protein-tyrosine phosphate (PTP1B) [13] inhibitors and used in the treatment of leishmaniasis [14] and the active arthritis [15]. Furthermore the isoxazolones are used for the development of optical storage [16], nonliner optical research [17], ligh-conversion molecular devices [18] and filter dyes in photographic films [19].

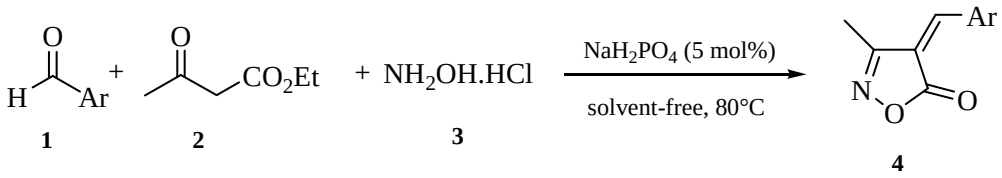
On the other hand, isoxazolones are an important class of intermediates of synthesis [20]. They can undergo N-alkylation reactions [21] or be transformed into quinolines [22]. Isoxazolones can also undergo various cycloaddition reactions [23].

For these reasons, several methods of access to this important class of compounds are reported in the literature. The most common method for the synthesis of 3,4-disubstituted isoxazolones is the one-pot three-component polycondensation reaction between hydroxylamine hydrochloride, an aromatic aldehyde and ethyl acetoacetate catalyzed by various catalyst such as sodium benzoate [24], sodium silicate [25], sodium sulfite [26], nanoparticles and heteropolyacids [27]. Various other successful methods such as the use of sodium acetate under visible light [28], pyridine under ultrasonic irradiations [29] and Fe_2O_3 and $H_3PW_{12}O_{40}$ under microwave irradiation [27]. The use of sodium ascorbate [30], sodium citrate [31], sodium saccharin [32], sodium tetraborate [33] and tartaric acid [34] as environmentally friendly catalysts have been also reported.

Some other methods for preparing the isoxazolones involve reactions in two successive steps by first the synthesis of 3-methyl-isoxazol-5(4H)-ones from condensation of hydroxylamine hydrochloride and ethyl acetoacetate followed by action on aromatic aldehydes [13, 35] have been described. Two specific methods for synthesizing isoxazolones, one by the action of hydroxylamine on carbamates and the other which was carried out from condensation of (chlorocarbonyl)phenyl ketene with benzhydroxamic acids have also been reported [21, 36].

In continuation of our research of new, simple, efficient, inexpensive and environmentally friendly procedures [37-40], we propose herein the use of sodium dihydrogen phosphate, an eco-friendly reagent, non-explosive, non-toxic

because it is used as a food additive, available, inexpensive, previously used in the synthesis of substituted imidazoles [41], as catalyst in the preparation of a series of isoxazolones in a solvent free medium (Scheme 1):



1 **2** **3** **4**

Scheme1: 4-arylidene-3-methylisoxazol-5(4*H*)-ones synthesis

MATERIALS AND METHODS

All specified solvents and reagents were of reagent grade and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 on a BRUKER AVANCE DPX spectrometer at 250 and 62.9 MHz respectively using TMS as internal standard. Chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). IR spectra were obtained on potassium bromide (KBr) pellets with a Shimadzu FT IR-8201 PC spectrometer. Melting points were determined in a capillary tube and are uncorrected.

General procedure:
In a 25 ml flask equipped with a magnetic stirrer are placed 2 mmol of aromatic ou heterocyclic aldehyde, 2 mmol of hydroxylamine hydrochloride, 2 mmol of ethyl acetoacetate and 5 mol% of sodium dihydrogen phosphate as catalyst. The mixture is heated at 80° C for the necessary time (see Table 3), the reaction being monitored by TLC. When the reaction is judged complete, the mixture was gradually poured into ice water. Stirring is continued a few minutes and then filtered. The solid obtained is purified by crystallization from ethanol.

Data for selected products:

4-benzylidene-3-methylisoxazole-5(4*H*)-one (4a): ^{1}H NMR (DMSO-d_6, δ ppm, *J* Hz): 3.11 (s, 3H, CH_3), 7.38-7.54 (m, 3H), 7.6 (s, 1H, CH=C), 8.4 (d, 2H, *J* = 7.93). ^{13}C NMR (DMSO-d_6, δ ppm): 11 (CH_3), 127, 130, 133, 134, 150 (CH=C), 160 (C=N), 169 (C=O). IR (KBr-cm^{-1}): v_{max}=3452, 3058, 2854, 1739, 1616, 1384, 1114.

4-(2-methoxybenzylidene)isoxazol-5(4*H*)-one (4c): ^{1}H NMR (DMSO-d_6, δ ppm, *J* Hz): 3 .11 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 7.08 (t, 1H, *J* = 7.33), 7.19 (d, 1H, *J* = 8.28), 7.6 (d, 1H , *J* = 7.41), 8.05 (s, 1H), 8.6 (d, 1H, *J* = 7.71). ^{13}C NMR (DMSO-d_6, δ ppm): 11 (CH_3), 60 (OMe), 114, 120, 122, 125, 128, 134, 140 (CH=C), 164 (C=N), 169 (C=O). IR (KBr-cm^{-1}): v_{max}=3348, 2854, 1735, 1604, 1107, 1481.

4-(4-(dimethylamino)benzalidene)-3 methylisoxazol-5 (4*H*)-one (4d): ^{1}H NMR (DMSO-d_6 ,δ ppm, *J* Hz): 2.16 (s, 3H, CH_3), 3.10 (s , 6H, $2CH_3$) , 6.7 (d, 2H, *J* = 8.21), 7.4 (s, 1H, CH=C), 8.33 (d, 2H, *J* = 7.64) . ^{13}C NMR (DMSO-d_6,δ ppm): 11 (CH_3), 40 (2 CH_3), 127, 130, 133, 134, 150 (CH=C), 162 (C=N), 169 (C=O). IR (KBr-cm^{-1}): v_{max}=3116, 2881, 1627, 1384, 1114.

4-(4-chlorobenzylidene)-3-methylisoxazol-5(4*H*)-one (4e): ^{1}H NMR (DMSO-d_6, δ ppm, *J* Hz): 3.11 (s, 3H, CH_3), 7.67 (d, 2H, *J* = 8.53), 7.95 (s, 1H, CH=C), 8.42 (d, 2H, *J* = 8.58). ^{13}C NMR (DMSO-d_6, δ ppm): 11 (CH_3), 128, 134, 133, 164.6 (C=N), 168.3 (C=O). IR (KBr-cm^{-1}): v_{max}= 3394, 1732, 1626, 1492, 1388, 825.

3-methyl-4-(4-methylbenzylidene)isoxazol-5(4*H*)-one (4i): ^{1}H NMR (DMSO-d_6, δ ppm, *J* Hz): 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.5 (s, 1H, CH=C), 7.3 (d, 2H, *J* = 8.09), 8.3 (d, 2H, *J* = 8.2). ^{13}C NMR (DMSO-d_6, δ ppm): 11 (CH_3), 22 (CH_3-Ar), 128, 130, 140, 150 (CH=C), 162 (C=N), 169 (C=O). IR (KBr-cm^{-1}): v_{max}=3244, 1735, 1631, 1388, 1118.

4-(thiophen-2-ylmethylene)isoxazol-5-(4*H*)-one (4k): ^{1}H NMR (DMSO-d_6, δ ppm, *J* Hz): 3.4 (s, 3H, CH_3), 7.3 (d, 1H, *J* = 3.97, CH=C) , 8.10-8.17 (m, 3H).^{13}C NMR (DMSO-d_6, δ ppm): 11 (CH_3), 114, 126, 131, 143 (CH=C), 161 (C=N), 169 (C=O). IR (KBr-cm^{-1}): v_{max}= 3105, 2862, 1735, 1617, 1404, 1120, 664.

RESULTS AND DISCUSSION

The study is made on the basis of a condensation reaction model between benzaldehyde (**1**), ethyl acetoacetate (**2**) and hydroxylamine hydrochloride (**3**) in the respective proportions of 1/1/1 and an amount of 10 mol% of sodium dihydrogen phosphate (NaH_2PO_4) as catalyst.

In a first step, we examined the reaction in various solvents such as H_2O, EtOH, CH_3CN, EtOH / H_2O (1: 1), CH_2Cl_2 and in a solvent-free medium at different temperatures: from ambient, 50C°, 80°C (solvent-free) to reflux. The results gathered in Table 1 show that the products are obtained with yields ranging between 8 and 73%. The best result was achieved without the use of solvent (Table 1, entry 8).

Table 1: Effect of solvent and temperature

Entry	Solvent	Catalyst (mol%)	Time (h)	T (°C)	Yield (%)
1	H_2O	10	3	Ambiant	8
2	H_2O	10	3	50°C	60
3	H_2O	10	3	Reflux	62
4	EtOH	10	3	Reflux	50
5	EtOH/ H_2O	10	3	Reflux	54
6	CH_2Cl_2	10	3	Reflux	No reaction
7	CH_3CN	10	3	Reflux	56
8	-	10	3	80°C	73

[a]Reactions conditions: benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), NaH_2PO_4 (0.1 mmol). [b]Isolated yields of pure product.

In order to determine the optimum amount of the catalyst, we performed in a second step, several other reactions, by carrying out the previous condensation without solvent at 80 °C with various amounts of catalyst increasing from 5, 20, 30 to 50 mol%. The results summarized in Table 2 show that condensations with 10, 20, 30 and 50 mol% of sodium dihydrogen phosphate give yields of 73, 72, 65, 66% respectively. However, an amount of 5 mol% gave a significantly higher yield (80%) (Table 2, entry 1). Therefore the optimal conditions for this condensation are 5 mol% of NaH_2PO_4 in solvent-free medium.

Table 2: Effect of catalyst

Entry	NaH_2PO_4 (mol%)	Time (h)	T (°C)	Yield (%)
1	5	2.5	80°C	80
2	10	3	80°C	73
3	20	3	80°C	72
4	30	2	80°C	65
5	50	3	80°C	66

[a] Reactions conditions: Aromatic aldehydes (1 mmol), ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), NaH_2PO_4, solvent-free. [b]Isolated yields of pure product.

Given these results and to show the generality of the reaction, we applied the optimized reaction conditions for the synthesis of isoxazolones to a variety of substituted aromatic and heteroaromatic aldehydes. The obtained results are summarized in the table below (Table 3).

Table 3 shows that the expected products are obtained with good to excellent yields in relatively short reaction time compared to those reported in the literature, and without formation of by-products. Table 3 shows also that whatever the nature and the position of the substituent, yields remain good to excellent. It nevertheless noted that the best performance is obtained with 2-methoxybenzaldehyde (97%, Table 3, entry 3), 4-chlorobenzaldehyde (97%, Table 3, entry 5), and 4-hydroxybenzaldehyde (97%, Table 3, entry 8).

Table 3: Synthesis of 4-arylidene-3-methylisoxazol-5(4*H*)-ones catalyzed by NaH_2PO_4

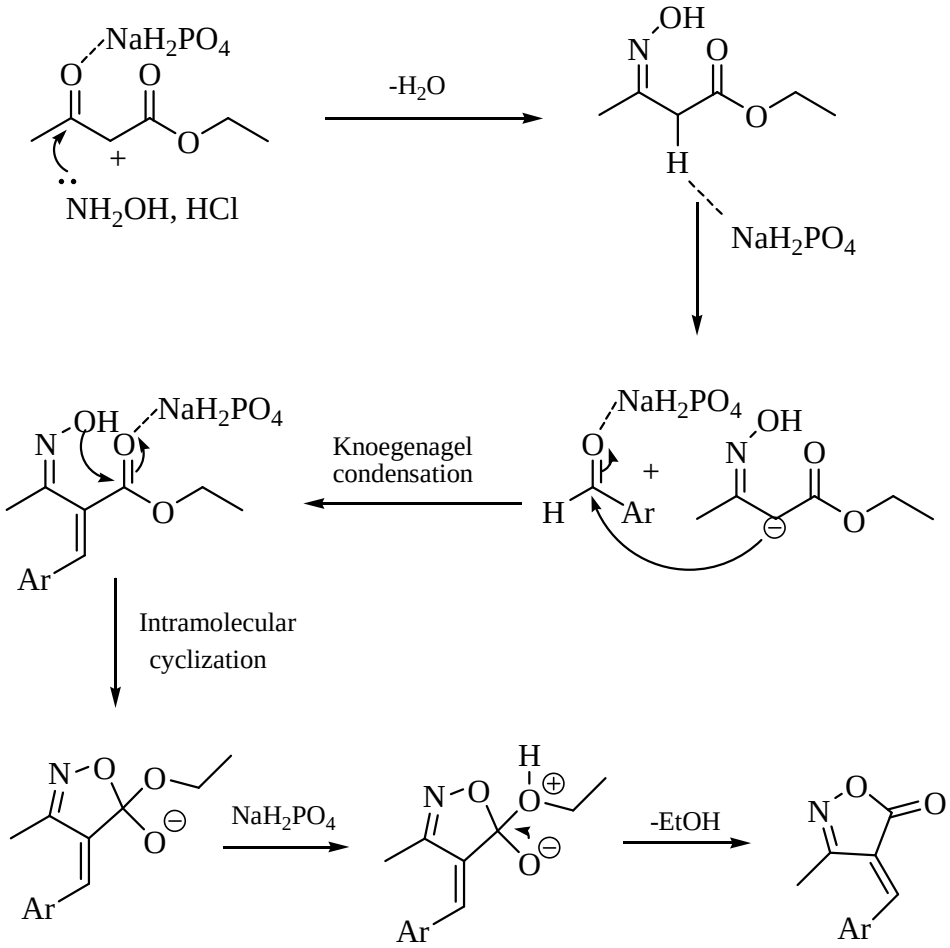
Entry	Product[a]	Ar	Time (h)	Yield[b] (%)	Mp (°C)	Mp °C (Lit.)
1	**4a**	C_6H_4	3	80	139-141	140-142[32]
2	**4b**	4-$O_2NC_6H_4$	5	66	166-167	163-165[42]
3	**4c**	2-$MeOC_6H_4$	3	97	151-152	159-160[42]
4	**4d**	4-$(Me)_2NC_6H_4$	3	60	208-210	208-209[27]
5	**4e**	4-ClC_6H_4	3	97	126-128	128-130[34]
6	**4f**	4-MeC_6H_4	3	68	130-132	130-132[33]
7	**4g**	2-HOC_6H_4	3	73	202-204	200-202[42]
8	**4h**	4-HOC_6H_4	5	97	221-223	214-216[42]
9	**4i**	4-$MeOC_6H_4$	3	96	175-177	177-179[42]
10	**4j**	3-Indolyl	1	98	238-240	239-241[17]
11	**4k**	2-Thienyl	3	92	143-145	144-146[33]

[a] Reactions conditions: Aromatic aldehydes (2 mmol), ethyl acetoacetate (2 mmol), hydroxylamine hydrochloride (2 mmol), NaH_2PO_4 (0.05 mmol), solvent-free. [b]Isolated yields of pure products.

Heterocyclic aldehydes such as indole-3-carbaldehyde and thiophene-2-carbaldehyde also give excellent yields of 98% and 92% (Table 3, entries 10 and 11).

Finally the reaction gave good results with both substituted aromatic aldehydes having electron-donating or electron-withdrawing groups, or heterocyclic aldehydes.

In scheme 2 we propose a plausible mechanism for the formation of isoxazolones based on the acidic and basic properties of the catalyst.



Scheme 2: plausible mechanism of 4-arylidene-3-methylisoxazol-5(4*H*)-ones synthesis

Initially, there is a classical reaction between hydroxylamine and the carbonyl function of ethyl acetoacetate leading to an oxime: the sodium dihydrogen phosphate can make this step easier by the protonation of the carbonyl function. The second step is a type of Knoevenagel reaction leading to benzylydene: this step can also be helped by the catalyst that can play both the role of proton donor and acceptor, depending on demand. The reaction proceeds by an intramolecular cyclization followed by loss of a molecule of EtOH to yield the final product.

CONCLUSION

In summary, we have described a new simple procedure, efficient, environmentally friendly isoxazolones synthesis by the use of sodium dihydrogen phosphate as a catalyst for polycondensation between an aromatic aldehyde, hydroxylamine hydrochloride and ethyl acetoacetate in a solvent free medium. Besides the fact that the catalyst is not dangerous, available, inexpensive, the yields are high and reactions time are short.

REFERENCES

[1]Patrizia, D.; Carbone, A.; Barraja, P.; Kelter, G. ; Fieberg, H. H. ; Cirrincone, G. *Bioorg. Med. Chem.* **2010**, *18*, 4524.
[2]Prashanthi, A.; Kiranmai, K.; Subha shini, N. J. P.; Shiraraj. *Spectrochim. Acta A.* **2008**, *70*, 30.
[3]Padmaja, A.; Rajasekhar, C.; Muranikrishna, A.; Padmavathi, V. *Eur. J. Med. Chem.* **2011**, *46*, 5034.
[4]Karabasanakouda, T.; Adhikari, A. V.; Girisha, M. *Indian J. Chem.* **2009**, *48B*, 430.
[5]Lee, Y. S.; Park, S. M.; Kim, B. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1126.

[6]Mao, J.; Yuan, H.; Wan, B.; Pak, D.; He, R.; Franzblau, S. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1263.
[7]Santos, M. M. M.; Faria, N.; Iley, J. ; Coles, S. J. ; Hursthouse, M. B. ; Martins, M. L. ; Moreira, R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 193.
[8]Srinivas, A.; Nagaraj, A.; Reddy, C. S. *Eur. J. Med. Chem.* **2010**, *45*, 2353.
[9]Changtam, C.; Hongmance, P.; Suksamram, A. *Eur. J. Med. Chem.* **2010**, *45*, 4446.
[10]Kamal, A.; Bharathi, E. V.; Reddy, J. S.; Janaki, M; Ramaiah, D.; Reddy, M. K.; Viswanath, A.; Reddy, T. L. ; Shaik, T. B.; Pushpavali, S. N. C. V. L. Bhadra, M. P. *Eur. J. Med. Chem.* **2011**, *46*, 691.
[11]Kano, H.; Adachi, I.; Kido, R.; Hirose, K. *J. Med. Chem.* **1967**, *10*, 411.
[12]Talley, J. J.; Brown, D. L.; Carter, J. S. and all. *J. Med. Chem.* **2000**, *43*, 775.
[13]Kafle, B.; Cho, H. *Bull. Korean Chem. Soc.* **2012**, *33*, 275.
[14]Suryawanshi, S. N.; Tiwari, A.; Chandra, N.; Cupta, R. S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6559.
[15]Knecht, W.; Loffler, M. *Biochem. Pharmacol.* **1998**, *56*, 1259.
[16] Zhang, X. H.; Wang, L. Y.; Zhan, Y. H.; Fu, Y. L.; Zhaia, G. H.; Wenc, Z. Y. *J. Mol. Struct.*, **2011**, *994*, 371.
[17] Zhang, X.-H.; Zhan, Y.-H.; Chen, D;. Wang, F;. Wang, L.-Y. *Dyes Pigments*, **2012**, *93*, 1408.
[18]Pu, S.; Li, H.; Liu, G.; Liu, W.; Cui, S.; Fan, C.; Cui, S. *Tetrahedron* **2012**, *68*, 2267.
[19]Aret, E.; Meekes, H.; Vlieg, E.; Deroover, G. *Dyes Pigments*, **2007**, *72*, 339.
[20]Batra, S.; Bhaduri, A. P. *J. Indian Inst. Sci.* **1994**, *74*, 213 and references therein.
[21]Molla Ibrahimio, A. R. *S. Afr. J. Chem.* **2012**, *65*, 104.
[22]Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *Tetrahedron* **2003**, *59*, 9887.
[23]Badrey, M. G.; Gomha, S. M. *J. Pharm. Pharm. Sci.* **2014**, *6*, 236.
[24] Liu, Q.; Zhang, Y.-N. *Bull. Korean Chem. Soc.* **2011**, *32*, 3559.
[25] Liu, Q.; Wu, R.-T. *J. Chem. Res.* **2011**, 598.
[26] Liu, Q.; Hou, X. *Phosphorus Sulfur Silicon Relat. Elem.* **2012**, *187*, 448.
[27]Fozooni, S.; Hosseinzadeh, N. G. ; Hamidian, H. ; Akhgar, M. R. *J. Bras. Chem. Soc.* **2013**, *24*, 1649.
[28]Saikh, F.; Das, J.; Ghosh, S. *Tetrahedron Lett.* **2013**, *54*, 4679.
[29]Ablagan, K.; Xiamuxi, H. *Synth. Commun.* **2012**, *42*, 1128.
[30] Kiyani, H. *Org. Chem. Indian J.* **2013**, *4*, 97.
[31]Kiyani, H.; Ghorbani, F. *Heterocycl. Lett.* **2013**, *3*, 145.
[32] Kiyani, H.; Ghorbani, F. *OJOC*, **2013**, *1*, 5.
[33] Kiyani, H.; Ghorbani, F. *Heterocycl. Lett.* **2013**, *3*, 359.
[34]Khandebharad Amol, U.; Sarda Swapnil, R.; Gill Charansingh, H.; Agrawal Brijmohan R. *Res. J. Chem. Sci.* **2015**, *5*, 27.
[35]Villemin, D. ; Martin, B.; Garrigues, B. *Synth. Commun.* **1993**, *23*, 2251.
[36]Nejadshafiee, V.; Saidi, K.; Abaszadeh, M. *Bull. Korean Chem. Soc.* **2011**, *32*, 4176.
[37]Amine Khodja, I; Ghalem, W.; Boulcina, R.; Boumoud, T.; Debache, A. *Der Pharma Chem.* **2015**, *7*, 175.
[38]Ghalem, W.; Sedrati, R. H.; Benloucif, N.; Berrée, F.; Boumoud, B.; Debache, A. *Lett. Org. Chem.* **2013**, *10*, 150.
[39] Amine Khodja, I.; Ghalem, W.; Dehimat, Z.; Boulcina, R.; Carboni, B.; Debache, A. *Synth. Commun.*, **2014**, *44*, 959.
[40]Amine Khodja, I.; Boulcina, R.; Debache, A. *Lett. Org. Chem.*, **2015**, *12*, 77.
[41] Karimi-Jaberi, Z.; Barekat, M. *Chin. Chem. Lett.* **2010**, *21*, 1183.
[42]Setamdideh, D. *J. Mex. Chem. Soc.* **2015**, *59*, 191.