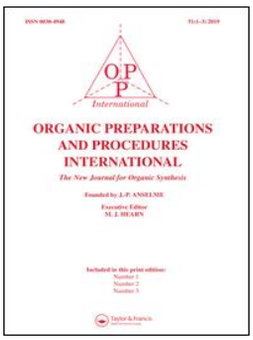

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OPPI BRIEF

Facile Synthesis and Antioxidant Evaluation of 4-Arylmethylideneisoxazol-5(4*H*)-ones

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Isoxazolone derivatives show significant biological and medicinal properties.[1–7] They constitute excellent intermediates for the synthesis of numerous heterocycles and undergo several chemical transformations.[8–10] A literature review shows that the best method for the synthesis of these molecules is a three-component reaction among aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride under different catalysts and conditions.[11]

In continuing our research on new simple and environmentally friendly procedures for the preparation of heterocycles by multi-component reactions,[12–14] we now report the synthesis of 4-arylmethylideneisoxazol-5(4*H*)-ones by the reaction among aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride catalyzed by K_2CO_3. This commonly available base is very inexpensive, well-tolerated in organic agriculture, and safe; it has found wide use in numerous chemical transformations.[15–19] *Scheme 1* below shows the approach taken.

We chose as our model system an equimolar mixture of 4-hydroxybenzaldehyde, ethyl acetoacetate and hydroxylamine chloride in a reaction catalyzed by different amounts of K_2CO_3. The selected model was subjected to different solvent and temperature conditions, as shown in *Table 1*. The best result was observed in Entry 8, with 5 mol% catalyst in water at reflux for an hour (see Experimental Section).

The optimum reaction conditions were applied to a number of aromatic and heteroaromatic aldehydes bearing different substituents. The results are summarized in *Table 2*. Reaction times were determined by thin layer chromatography in each case. Whatever the position of the substituent, yields were generally good to very good (between 64% and 85% and an average of 69%). Compounds **4k-4m** are novel and reported here for the first time.

Antioxidant Activity

The antioxidant activity of some of the compounds (**4i-4m**) was determined using four complementary methods: The 1,1-diphenyl-2-pycrilhydrazil (DPPH) free radical

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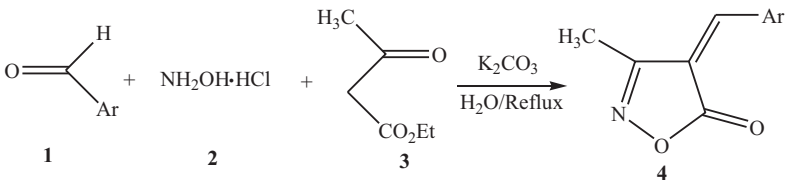

Scheme 1. K_2CO_3-catalyzed synthesis of 3-methyl-4-arylmethylidene-isoxazol-5(4*H*)-ones.

scavenging assay, the cupric reducing antioxidant capacity assay, the β-carotene-linoleic acid assay and the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) scavenging assay. The results are summarized in *Table 3*.

We observe that all the studied molecules had at least some activity, however the best results were obtained with **4i** and **4k** for the DPPH assay ($IC_{50} = 35.91 \pm 2.23$ and 64.00 ± 0.48) and with 4i and 4m in the CUPRAC assay ($A_{0.50} = 10.86 \pm 0.49$ and 11.18 ± 1.59).

In this report, we describe a three-component reaction among aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride for the synthesis of 3-methyl-4-arylmethylidene-isoxazol-5(4*H*)-ones in good to very good yields. The process is catalyzed by potassium carbonate, a universally available and inexpensive reagent that is easy to handle and comparatively green. The chief merits of our method are its simplicity, convenience and low cost. We examined the antioxidant activity of some of the new derivatives and found significant activity. We hope that our results will stimulate further exploration in this interesting area.

Experimental Section

Chemistry

The solvents and reagents were used as received from commercial sources. ^1H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE DPX spectrometer at 250.13 and 62.5 MHz respectively, using TMS as an internal reference. Chemical shifts are expressed in parts per million (ppm) and the coupling constants (*J*) in Hertz (Hz). IR spectra were obtained as potassium bromide (KBr) pellets with a Shimadzu FT IR-8201 PC spectrometer. The reaction monitoring was accomplished by layer chromatography (TLC) which was carried out using 0.2 mm Kieselgel F_{254} silica plates (Merck) with hexane/ethyl acetate (8/2) as eluting solvent. Mass spectrometry was performed on Brucker MaXis 4G using ESI technique. Because of their low volatility, it was not possible to obtain elemental analyses for the new boron compounds, their HRMS are given.

*General Procedure for 3-methyl-4-arylmethylidene-isoxazol-5(4*H*)-one Synthesis (4a-m)*

One mmol of the aldehyde, 1 mmol of hydroxylamine hydrochloride, 1 mmol of ethyl acetoacetate and 5 mol% of K_2CO_3 are mixed in a 25 ml flask equipped with a magnetic stirrer. The mixture is refluxed in 5 ml of water for the time required (see *Table 2*), followed by TLC. When the reaction is judged to be finished, the mixture is gradually poured into ice-cold water. The stirring is maintained for a few minutes and the

Table 1
Optimization of Reaction Conditions

Entry	Solvent	Catalyst (mol%)	Time (h)	Temperature (°C)	Yield (%)
1	H_2O	10	24	ambient	78
2	H_2O	10	1	reflux	83
3	EtOH	10	1	reflux	44
4	EtOH/H_2O (1/1)	10	1	reflux	traces
5	CH_2Cl_2	10	1	reflux	traces
6	CH_3CN	10	1	reflux	–
7	–	10	1	80	42
8	H_2O	5	1	reflux	83
9	H_2O	15	1	reflux	79
10	H_2O	20	1	reflux	78
11	H_2O	30	1	reflux	76

Table 2
K_2CO_3-catalyzed Synthesis of Compounds (**4a-m**)

Entry	Ar	Product	Time (h)	Yield[a] %	Mp °C	Mp °C (Lit.)
1	C_6H_5-	4a	3	70	142–144	140–142[24]
2	4-ClC_6H_4-	4b	4	76	128–130	128–130[25]
3	4-MeC_6H_4-	4c	3	72	130–132	129–132[24]
4	4-$MeOC_6H_4$-	4d	1	83	175–177	175–177[24]
5	2-$MeOC_6H_4$-	4e	2	85	151–152	159–160[27]
6	4-HOC_6H_4-	4f	2.5	80	222–224	214–216[24]
7	4-$(Me)_2NC_6H_4$-	4g	2	73	208–210	206–209[24]
8	2-Thienyl	4h	3	72	144–146	146–147[25]
9	3-$MeOC_6H_4$-	4i	3	77	130–132	130–132[26]
10	2-MeC_6H_4-	4j	4	41	100–102	99–101[28]
11	2-$(HO)_2BC_6H_4$-	4k	3	40	>260	This work
12	4-$(HO)_2BC_6H_4$-	4l	4	68	>260	This work
13	3-$(HO)_2B$-2-$MeOC_6H_4$-	4n	4	66	>260	This work

[a]Isolated yield.

obtained solid is filtered and purified by crystallization from ethanol. Spectrometric data for selected compounds are provided below.

4-Benzylidene-3-methylisoxazol-5(4H)-one (4a)

^{1}H NMR (DMSO-d_6): 2.4 (s, 3H, CH_3), 7.42–7.66 (m, 5H), 8.2 (s, 1H, CH = C). ^{13}C NMR (DMSO-d_6): 11.18 (CH_3), 118.82, 119.34, 128.46, 131.91, 133.38, 133.52, 150.41 (CH = C), 161.11 (C = N), 167.46 (C = O). IR (cm^{-1}): ν_{max} = 756, 1181, 1523, 1624, 1739, 2858.

Table 3
Antioxidant Activity of Compounds (**4i-4m**)

	Antioxidant activity[a]			
Product	DPPH· assay IC_{50} (μg/ml)	$ABTS^{\cdot+}$ assay IC_{50} (μg/ml)	β-Carotene-linoleic acid assay IC_{50} (μg/ml)	CUPRAC assay $A_{0.50}$ (μg/ml)
4i	35.91 ± 2.23	10.00 ± 0.10	>200	10.86 ± 0.49
4j	77.67 ± 0.62	90.51 ± 0.59	>200	16.34 ± 0.47
4l	64.00 ± 0.48	14.33 ± 0.68	175.80 ± 1.20	11.79 ± 1.11
4l	75.53 ± 3.02	16.68 ± 0.15	73.84 ± 1.09	18.13 ± 2.88
4m	134.03 ± 3.63	19.38 ± 1.14	>200	11.18 ± 1.59
BHT[b]	22.32 ± 1.19	1.29 ± 0.30	1.05 ± 0.01	9.62 ± 0.87
BHA[b]	5.73 ± 0.41	1.81 ± 0.10	0.90 ± 0.02	3.64 ± 0.19

[a]Values expressed are means ± S.D. of three parallel measurements. ($p < 0.05$).
[b]Reference compounds.
BHA: Butylhydroxyanisole, BHT: Butylhydroxytoluene.

4-(4-Methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4d)

^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 3.95(s, 3H, OCH_3), 7.01 (d, 2H, $J = 7.5$), 7.38 (s, 1H, CH = C), 8.44 (d, 2H, $J = 7.5$). ^{13}C NMR (DMSO-d_6): 11.72 (CH_3), 55.79 (OCH_3), 114.72, 125.87, 137.06, 137.21, 149.56, 163.78 (C = N), 164.69 (C = O). IR (cm^{-1}): ν_{max} = 813, 1218, 1550, 1593, 1720, 2935.

4-(2-Methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4e)

^{1}H NMR (DMSO-d_6): 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 (t, 1H, $J = 7.41$), 8.05 (s, 1H), 8.6 (d, 1H, J =7.71). ^{13}C NMR (DMSO-d_6): 11.30 (CH_3), 56.32 (O-CH_3), 111.86, 117.96, 119.94, 120.56, 120.38, 132.44, 136.64, 144.86 (CH = C), 162.14 (C = N), 168.05 (C = O). IR (cm^{-1}): ν_{max} = 860, 1373, 1550, 1593, 1728.

4-(4-Hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4f)

^{1}H NMR (DMSO-d_6): 3.2 (s, 3H, CH_3), 6.85 (d, 2H, $J = 8.2$), 7.35 (s, 1H, CH = C), 8.25 (d, 2H, $J = 8.2$), 10.5 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): 11.23 (CH_3), 113.95, 116.06, 124.26, 134.41, 137.21, 150.20, 163.78 (C = N), 168.69 (C = O). IR (cm^{-1}): ν_{max} = 813, 1172, 1550, 1593, 1728, 2935, 3741.

3-((3-Methyl-5-oxoisoxazol-4(5H)-ylidene)methyl)phenylboronic acid (4k)

^{1}H NMR (DMSO-d_6): 2.55(s, 3H, CH_3), 7.56 (t, 1H, $J = 7.2$), 7.97 (s, 1H_{Ar}), 8,03 (dd,1H_{Ar}, J = (7.2, 2.2), 8.2 (s, 2H, 2OH) 8.52 (s, 1H, CH = C), 8.66 (dd, 1H_{Ar}, J = (7.2, 2.2). ^{13}C NMR (DMSO-d_6): 11.73 (CH_3), 118.91, 128.39, 132.11, 134.46, 139.83, 141.17, 152.76, 162 .71 (C-CH3), 168.2 (C = O). IR (cm^{-1}): ν_{max} = 686, 1161, 1566,

1608, 1751, 2931, 3363. HRMS (MS-ESI, m/z): $[M + Na]^+$ calculated for ($C_{11}H_{10}BNO_4Na^+$) 254.06006, found 254.0607.

4-((3-Methyl-5-oxoisoxazol-4(5H)-ylidene)methyl)phenylboronic acid (4l)

^{1}H NMR (DMSO-d_6): 2.3 (s, 3H, CH_3), 7.8-8.05 (m, 3H, 2OH, CH = C), 8.24–8.47 (m, $4H_{Ar}$). ^{13}C NMR (DMSO-d_6): 11.33 (CH_3), 119.14, 126.82, 128.34, 132.31, 133.60, 134.23, 134.58, 151.63 (CH = C). IR (cm^{-1}): ν_{max} = 773, 1006, 1335, 1612, 1719, 2360, 3309. HRMS (MS-ESI, m/z): $[M + Na]^+$ calculated for ($C_{11}H_{10}BNO_4Na^+$) 254.06006, found 254.0607.

4-Methoxy-3-((3-methyl-5-oxoisoxazol-4(5H)-ylidene)methyl)phenylboronic acid (4m)

^{1}H NMR (DMSO-d_6): 2.5 (s, 3H, CH_3), 3.9 (s, 3H, O-CH_3) 7.15 (d, 1H, $J = 7.6$), 8.01 (s, 2H, 2OH), 8,03 (d, $1H_{Ar}$, $J = 7.6$), 8.13 (s, $1H_{Ar}$), 8.55 (s, 1H, CH = C). ^{13}C NMR (DMSO-d_6): 11.20 (CH3), 56.20 (O-CH_3), 110.90, 117.70, 120.00, 138.20, 141.10, 142.00, 147.00, 158.70, 161.90 (C-CH3), 167.60 (C = O). IR (cm^{-1}): ν_{max} = 879, 1122, 1577, 1608, 1728, 2947, 3502. MS-ESI, m/z: $[M + Na]^+$ calculated for ($C_{12}H_{12}BNO_2Na^+$) 236.08588, found 236.0859.

Antioxidant Activity

Bioactivity measurements were carried out on a 96-well microplate reader, namely, a Perkin Elmer Multimode Plate Reader En Spire, at the Center for Biotechnology Research. 1,1-Diphenyl-2-picrylhydrazyl (DPPH), butyldhydroxylanisole (BHA), butylhydroxyltoluene (BHT), β-carotene, linoleic acid, polyoxyethylene sorbitan monopalmitate (Tween-40), Neocuproine, and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), were obtained from Sigma-Aldrich GmbH, Sternheim, Germany; copper (II) chloride, potassium persulfate, and ammonium acetate were obtained from Biochem Chemopharma.

The DPPH free radical-scavenging activity was evaluated by a slight modification of the well-documented method of Blois.[20] The ABTS free cation-radical scavenging activity was obtained by spectrophotometric analysis according to a slight modification of the method proposed by Re et al.[21] The β-carotene bleaching activity was determined by the β-carotene-linoleic acid system described by Miller[22] and the cupric-reducing antioxidant capacity (CUPRAC) was evaluated according to the method of Apak et al.,[23] with slight modifications.

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