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MULTI-COMPONENT ONE-POT SYNTHESIS OF NEW 3-ARYL-3,4-DIHYDRO-4-(3-METHYL-4-NITRO-5-ISOXAZOLYL)-METHYL-BENZO[*e*][1,3]-OXAZINE-2-ONES

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Abstract
A three component one-pot protocol has been developed for the synthesis of new isoxazolyl-1,3-benzoxazine-2-ones from commercially available materials.

Keywords: Knoevenagel Condensation, piperidine, cyclization, isoxazolyl-1,3-benzoxazine-2-ones, one-pot synthesis

Introduction

Multi-component reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation[1,2] and are of increasing importance in organic and medicinal chemistry.[3-5] In MCRs a high degree of molecular diversity can be introduced by variation of a single component at a time. Considering that, rapidity and diversity are key factors in modern drug discovery, MCR strategies offer significant advantages over conventional linear-type syntheses, owing to their exceptional synthetic efficiency.[6] MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production.

Heterocycles are widely used compounds both in pharmaceutical and agricultural fields.[7] Consequently, the development of methodologies useful for the assembly of these molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. Among the heterocycles, 1,3-benzoxazines constitutes an important class of heterocycles that have been explored for developing pharmaceuticals due to their wide variety of pharmacological activity.[8-10] Compounds bearing the isoxazole moiety are endowed with various types of biological activities.[11-13] Inspired by the biological profile of isoxazoles, and 1,3-benzoxazines and their increasing importance in pharmaceutical and biological fields, and as a sequel to our work[14-17] on isoxazole substituted heterocycles, it was concerned worthwhile to synthesize certain new isoxazolyl 1,3-benzoxazines to investigate their biological activity.

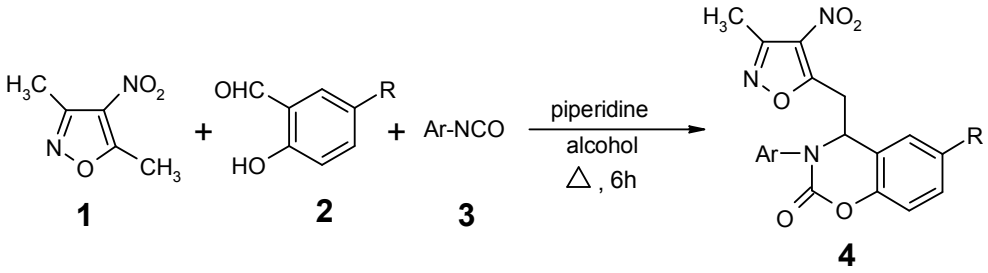
Our approach to the development of multi-component one-pot synthesis is based on the creation of building blocks containing several reactive centers which can be selectively reacted. To develop a diversity oriented synthesis using poly functional scaffolds such as 3,5-dimethyl-4-nitroisoxazole and salicylaldehyde and products with high pharmacological activity, we now

report a new one-pot, three component procedure (MCR-3), which allows the synthesis of isoxazolyl-1,3-benzoxazine-2-ones from commercially available materials.

Results and Discussion

Knoevenagel condensation of 3,5-dimethyl-4-nitroisoxazole **1** with salicylaldehydes **2** in presence of piperidine affords nitrostyrylisoxazoles **5**, which are further reacted *in situ* with aryl isocyanates **3** in the presence of piperidine to give addition product **6**, which ultimately undergoes cyclization by Michael type addition to give the title compounds *viz*., 3-aryl-3,4-dihydro-4-(3-methyl-4-nitro-5-isoxazolyl)-methyl-benzo[*e*][1,3]-oxazin-2-ones **4** in 60-70% yields by a multi-component one-pot synthesis (**Scheme-I**).

In a typical experiment, equimolar amounts of 3,5-dimethyl-4-nitroisoxazole **1** (0.01 mol), benzaldehyde **2** (0.01 mol) were reacted in the presence of piperidine (1 ml) in ethanol (15 ml) for 1 h at 80°C with stirring, and one equivalent of phenyl isocyanate **3** (0.01 mol) was added later and the refluxing continued for another 5 h at 80°C. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool. The solid that separated was collected by filtration, washed with pet ether and recrystallized from ethylacetate to give isoxazolyl 1,3-benzoxazines **4a**.



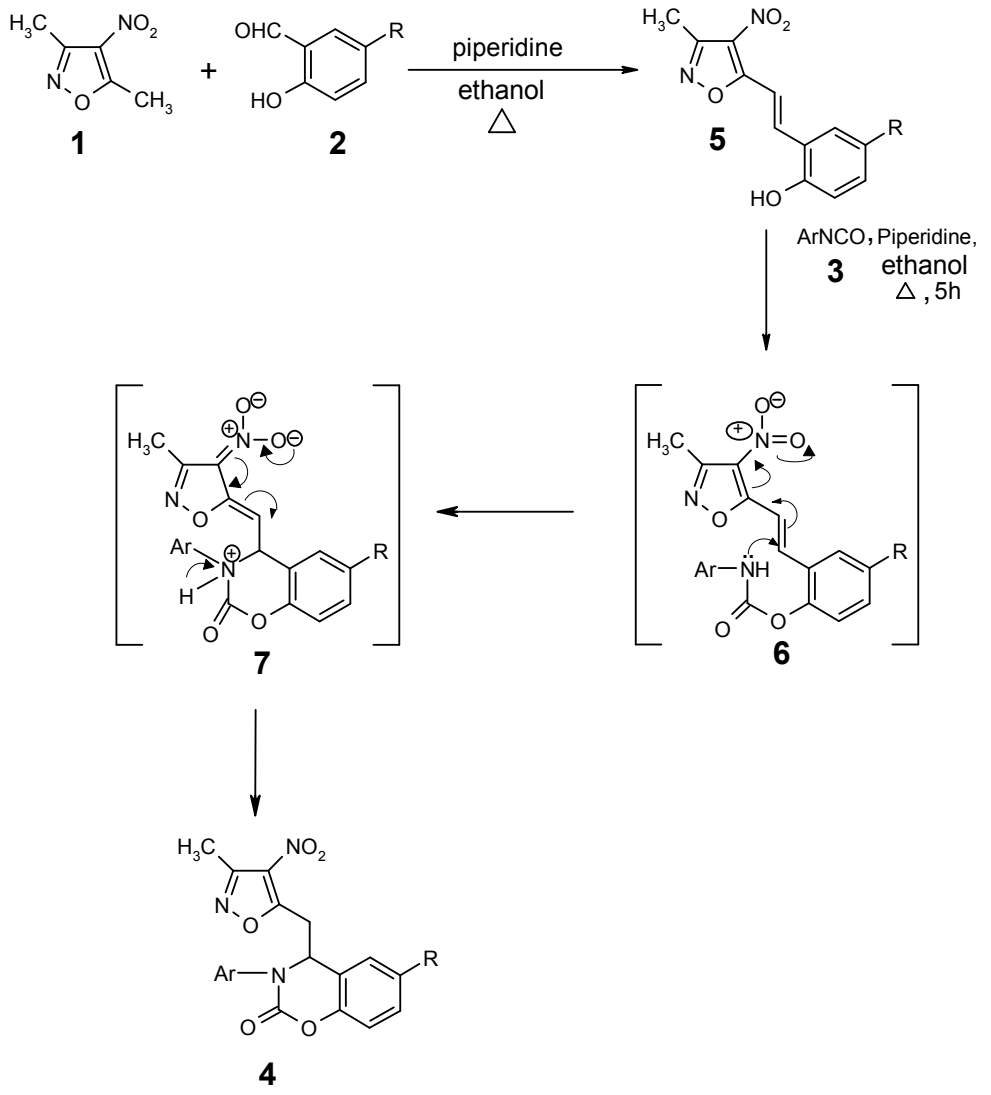
4a,	R=H,	Ar = C_6H_5
4b,	R=H,	Ar = 4-ClC_6H_4
4c,	R=H,	Ar = 4-BrC_6H_4
4d,	R=CH_3,	Ar = C_6H_5
4e,	R=CH_3,	Ar = 4-$CH_3C_6H_4$
4f ,	R=CH_3,	Ar = 4-ClC_6H_4
4g,	R=OCH_3,	Ar = C_6H_5
4h,	R=OCH_3,	Ar = 4-BrC_6H_4
4i,	R=OCH_3,	Ar = 4-$CH_3C_6H_4$
4j,	R=Cl,	Ar = C_6H_5
4k,	R=Cl,	Ar = 4-BrC_6H_4
4l,	R=Br,	Ar = C_6H_5
4m,	R=Br,	Ar = 4-ClC_6H_4

Scheme I

In order to study the scope of this reaction, different substituted benzaldehydes and aryl isocyanates were utilized in this multi-component synthesis. The desired product was obtained in each case with moderate to good yield. Finally, the results indicate that this synthetic strategy

permits the introduction of a diverse array of substituents on the benzene ring of aldehyde and isocyanate and the approach proved to be of general applicability.

The reaction mechanism involves the knoevenagel condensation of **1** with **2** in presence of piperidine to give nitrostyryl isoxazoles **5**, which may react with aryl isocyanate **3** to give the addition product **6**, which finally cyclises by a Michael type reaction to give the title compounds **4** (**Scheme-II**).



Scheme II

The IR spectra of isoxazolyl-1,3-benzoxazin-2-ones **4** exhibited characteristic absorption bands at 1725 and 1575, 1370 cm^{-1} due to carbonyl and nitro functional groups respectively. The ^1H NMR spectra of **4** displayed two prominent signals as a doublet and triplet around δ 3.4 and 5.0 due to CH_2 and CH protons respectively conforming cyclization process. The mass spectrum of **4a**, showed a molecular ion $[M+H]^+$ peak at m/z 366 supporting the product formation. The structures of compounds **4a-m** have been elucidated by elemental analyses, and spectral (IR, ^1H NMR, MS) data.

In conclusion, we reported the multi-component (MCR-3) one-pot protocol for the synthesis of isoxazolyl-1,3-benzoxazin-2-ones, using commercially available materials. This synthesis benefits from a simple method of purification, which does not require chromatography. This ease of purification compliments the one-pot synthesis, making the technology practical, easy to perform and facile. The biological activity of the products will be published elsewhere.

Experimental Section

Melting points are determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra was recorded in KBr on Perkin Elmer spectrum BX series FT-IR spectrometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using tetramethyl silane as internal standard and mass spectra on a Jeol JMC-300 spectrometer. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

Multi-component one-pot synthesis of 3-aryl-3,4-dihydro-4-(3-methyl-4-nitro-5-isoxazolyl)-methyl-benzo[*e*][1,3]-oxazin-2-ones 4a-m

To a stirred solution of 3,5-dimehtyl-4-nitroisoxazole **1** (0.01 mol) in ethanol (15 ml), were added piperidine (1 ml) and salicylaldehyde **2** (0.01 mol). The reaction mixture was refluxed with stirring at 80^{o}C for 1 h, and aryl isocyanate **3** (0.01 mol) was added later to the reaction mixture, heating continued at 80^{o}C for another 5 h. After the completion of the reaction (monitored by TLC) the reaction mixture was allowed to cool. The separated solid was filtered, washed with pet ether and recrystallized from ethyl acetate.

Compound 4a: IR (KBr): 1725 (CO), 1575, 1370 ($=N^+-O^-$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.3 (s, 3H, isoxazole-CH_3), 3.4 (d, 2H, CH_2), 5.0 (t, 1H, CH), 6.9-8.0 (m, 9H, Ar-H); MS (EI): m/z 366 $[M+H]^+$.

Compound 4b: IR (KBr): 1730 (CO), 1560, 1365 ($=N^+-O^-$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.2 (s, 3H, isoxazole-CH_3), 3.3 (d, 2H, CH_2), 5.1 (t, 1H, CH), 6.7-7.9 (m, 8H, Ar-H); MS (EI): m/z 400 $[M+H]^+$.

Compound 4c: IR (KBr): 1720 (CO), 1575, 1365 ($=N^+-O^-$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.3 (s, 3H, isoxazole-CH_3), 3.4 (d, 2H, CH_2), 4.9 (t, 1H, CH), 7.0-8.0 (m, 8H, Ar-H); MS (EI): m/z 444 $[M+H]^+$.

Compound 4d: IR (KBr): 1730 (CO), 1565, 1370 ($=N^+-O^-$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.2 (s, 3H, isoxazole-CH_3), 2.4 (s, 3H, Ar-CH_3), 3.5 (d, 2H, CH_2), 4.9 (t, 1H, CH), 7.0-8.0 (m, 8H, Ar-H); MS (EI): m/z 380 $[M+H]^+$.

Compound 4e: IR (KBr): 1725 (CO), 1560, 1370 ($=N^+-O^-$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.3 (s, 3H, isoxazole-CH_3), 2.4 (s, 6H, Ar-CH_3), 3.4 (d, 2H, CH_2), 5.0 (t, 1H, CH), 6.8-8.0 (m, 7H, Ar-H); MS (EI): m/z 394 $[M+H]^+$.

Compound 4f: IR (KBr): 1730 (CO), 1565, 1360 ($=N^+-O^-$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.2 (s, 3H, isoxazole-CH_3), 2.4 (s, 3H, Ar-CH_3), 3.5 (d, 2H, CH_2), 4.9 (t, 1H, CH), 6.7-7.9 (m, 7H, Ar-H); MS (EI): m/z 414 $[M+H]^+$.

Compound 4g: IR (KBr): 1725 (CO), 1570, 1365 ($=N^+-O^-$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.2 (s, 3H, isoxazole-CH_3), 3.4 (d, 2H, CH_2), 3.7 (s, 3H, OCH_3), 5.0 (t, 1H, CH), 6.8-7.9 (m, 8H, Ar-H); MS (EI): m/z 396 $[M+H]^+$.

Compound 4h: IR (KBr): 1730 (CO), 1570, 1360 ($=N^{+}-O^{-}$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.3 (s, 3H, isoxazole-CH_3), 3.5 (d, 2H, CH_2), 3.6 (s, 3H, OCH_3), 4.9 (t, 1H, CH), 6.7-8.0 (m, 7H, Ar-H); MS (EI): m/z 474 $[M+H]^{+}$.

Compound 4i: IR (KBr): 1725 (CO), 1575, 1370 ($=N^{+}-O^{-}$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.2 (s, 3H, isoxazole-CH_3), 2.4 (s, 3H, Ar-CH_3), 3.4 (d, 2H, CH_2), 3.6 (s, 3H, OCH_3), 4.9 (t, 1H, CH), 6.9-8.0 (m, 7H, Ar-H); MS (EI): m/z 410 $[M+H]^{+}$.

Compound 4j: IR (KBr): 1730 (CO), 1575, 1365 ($=N^{+}-O^{-}$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.3 (s, 3H, isoxazole-CH_3), 3.5 (d, 2H, CH_2), 4.9 (t, 1H, CH), 6.8-7.9 (m, 8H, Ar-H); MS (EI): m/z 400 $[M+H]^{+}$.

Compound 4k: IR (KBr): 1730 (CO), 1565, 1360 ($=N^{+}-O^{-}$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.2 (s, 3H, isoxazole-CH_3), 3.5 (d, 2H, CH_2), 4.9 (t, 1H, CH), 6.9-8.0 (m, 7H, Ar-H); MS (EI): m/z 478 $[M+H]^{+}$.

Compound 4l: IR (KBr): 1725 (CO), 1570, 1370 ($=N^{+}-O^{-}$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.3 (s, 3H, isoxazole-CH_3), 3.4 (d, 2H, CH_2), 5.0 (t, 1H, CH), 6.6-7.9 (m, 8H, Ar-H); MS (EI): m/z 444 $[M+H]^{+}$.

Compound 4m: IR (KBr): 1730 (CO), 1570, 1365 ($=N^{+}-O^{-}$) cm^{-1} ; ^{1}H NMR (300MHz, $CDCl_3$ δ ppm): 2.2 (s, 3H, isoxazole-CH_3), 3.5 (d, 2H, CH_2), 4.9 (t, 1H, CH), 6.7-7.9 (m, 7H, Ar-H); MS (EI): m/z 479 $[M+H]^{+}$.

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Table — I Characterization data of 3- aryl-3,4-dihydro-4-(3-methyl-4-nitro-5-isoxazolyl)-methyl-benzo[*e*][1,3]-oxazine-2-ones **4a-m**

Compd	R	Ar	M.P	Yield	Mol. Formula	Found (%) (Calcd)		
			(^{o}C)	(%)		C	H	N
4a	H	C_6H_5	138	66	$C_{19}H_{15}N_3O_5$	62.43 (62.46	4.17 4.14	11.47 11.50)
4b	H	4-ClC_6H_4	151	68	$C_{19}H_{14}N_3O_5Cl$	57.11 (57.08	3.50 3.53	10.54 10.51)
4c	H	4-BrC_6H_4	162	70	$C_{19}H_{14}N_3O_5Br$	51.33 (51.37	3.21 3.18	9.44 9.46)
4d	CH_3	C_6H_5	122	62	$C_{20}H_{17}N_3O_5$	63.29 (63.32	4.49 4.52	11.05 11.08)
4e	CH_3	4-$CH_3C_6H_4$	110	63	$C_{21}H_{19}N_3O_5$	64.09 (64.12	4.90 4.87	10.64 10.68)
4f	CH_3	4-ClC_6H_4	145	67	$C_{20}H_{16}N_3O_5Cl$	58.02 (58.05	3.87 3.90	10.19 10.15)
4g	OCH_3	C_6H_5	132	68	$C_{20}H_{17}N_3O_6$	60.80 (60.76	4.31 4.33	10.67 10.63)
4h	OCH_3	4-BrC_6H_4	128	70	$C_{20}H_{16}N_3O_5Br$	50.61 (50.65	3.43 3.40	8.89 8.86)
4i	OCH_3	4-$CH_3C_6H_4$	100	69	$C_{21}H_{19}N_3O_6$	61.64 (61.61	4.71 4.68	10.23 10.26)
4j	Cl	C_6H_5	148	61	$C_{19}H_{14}N_3O_5Cl$	57.11 (57.08	3.50 3.53	10.48 10.51)
4k	Cl	4-BrC_6H_4	173	63	$C_{19}H_{13}N_3O_5BrCl$	47.70 (47.67	2.71 2.74	8.81 8.78)
4l	Br	C_6H_5	160	65	$C_{19}H_{14}N_3O_5Br$	51.34 (51.37	3.16 3.18	9.50 9.46)
4m	Br	4-ClC_6H_4	165	68	$C_{19}H_{13}N_3O_5BrCl$	47.69 (47.67	2.77 2.74	8.75 8.78)

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