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One-Pot High-Throughput Synthesis of a 160-Membered Library of Methyl 3,5-Diaryl-isoxazoline-5-carboxylate Pharmacophores by a 2·2·2-Component Reaction

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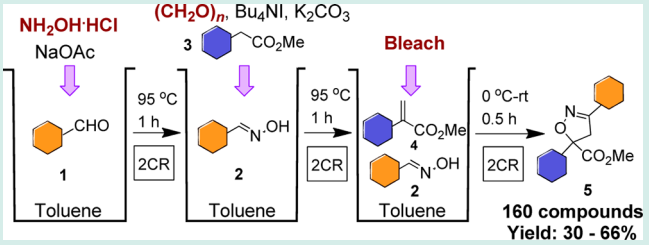
Supporting Information

ABSTRACT: A simple and efficient methodology has been developed for the synthesis of methyl 3,5-diaryl-isoxazoline-5-carboxylates in a high-throughput fashion. This was accomplished in one-pot by a sequence of three 2-component reactions steps (2·2·2-CR), whereby compounds were obtained in overall 30−66% isolated yields. The functional group diversity was established by synthesizing a 160-membered library.



KEYWORDS: *methyl 3,5-diaryl-isoxazoline-5-carboxylate, one-pot, high throughput, 1,3-dipolar cycloaddition, 2·2·2-component reaction*

INTRODUCTION

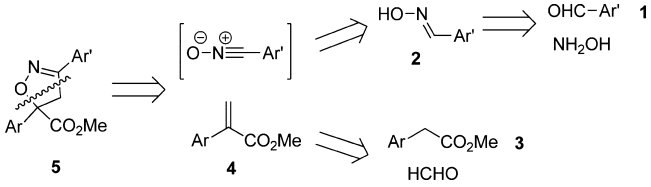
Isoxazolines have found extensive usage as pharmacophores in recent times. For example, isoxazoline derivatives have been reported as calcium release activated calcium (CRAC) channel modulators,[1] macrophage migration inhibitory factor (MIF) antagonists,[2] caspase inhibitors,[3] phophodiesterase-4 (PDE-4) inhibitors,[4] cell adhesion inhibitors,[5] cystic fibrosis transmembrane conductance regulator (CFTR) protein activators,[6] factor Xa inhibitors,[7] tubulin polymerization inhibitors,[8] inhibitors of matrix metalloproteinases and/or TNF-α converting enzyme,[9] and DNA methyltransferase 1 inhibitors.[10] Compounds containing isoxazoline moiety have been reported as potential antimicrobial, analgesic and antistress agents.[11] Isoxazolines are also useful synthons in organic synthesis and have been used for the synthesis of isoxazoles, β-lactams, γ-amino alcohols, and primary alcohols.[12] Key intermediates in the synthesis of Elliott's alcohol and resmethrins, Monatin, a natural sweetener, and natural products involve isoxazoline.[13]

In view of the wide ranging use of the isoxazoline moiety in organic and medicinal chemistry, a high throughput (HT) diversity oriented synthesis of this key scaffold could be of significant interest. We were particularly interested in a HT synthesis of 3,5-diaryl-isoxazoline-5-carboxylate derivatives as we intended to use the carboxylate group for further derivatization. Recently, synthesis of a 72-membered isoxazolino-β-ketoamide library by a 2·3-component reaction was reported.[14] However, this method was not amenable to modifications required for the synthesis of 3,5-diaryl-isoxazoline-5-carboxylate derivatives. We present here the synthesis of a 160-membered library of methyl 3,5-diaryl-isoxazoline-5-carboxylate pharmacophore by a modified HT synthesis. This involves a one-pot, sequential synthesis of an aryl oxime, a methyl 2-arylacrylate, an arylnitrile oxide, followed by a 1,3-dipolar cycloaddition between the methyl 2-arylacrylate and the arylnitrile oxide.

RESULTS AND DISCUSSION

Synthesis of isoxazolines by 1,3-dipolar cycloadditions between alkenes and a nitrile oxide is very well-known in organic synthesis.[15] There are several reports of library syntheses of isoxazolines from alkenes and nitrile oxides in both solution phase and on solid support.[16] However, in all these examples the oxime and the nitrile oxide precursor were preformed separately before reacting with the alkene. As seen in Scheme 1, the synthesis

Scheme 1. Retrosynthetic Analysis



of methyl 3,5-diaryl-isoxazoline-5-carboxylates can be considered as a composite of two sets of unrelated reactions synthesizing methyl 2-arylacrylate and arylnitrile oxide (generated in situ), followed by combining the products in the last step.

The initial proof-of-concept study focused on investigating the feasibility of achieving this multicomponent reaction in one-pot. Keeping in mind the scalability features and cost factors, we preferred a solution phase approach. Individually these are

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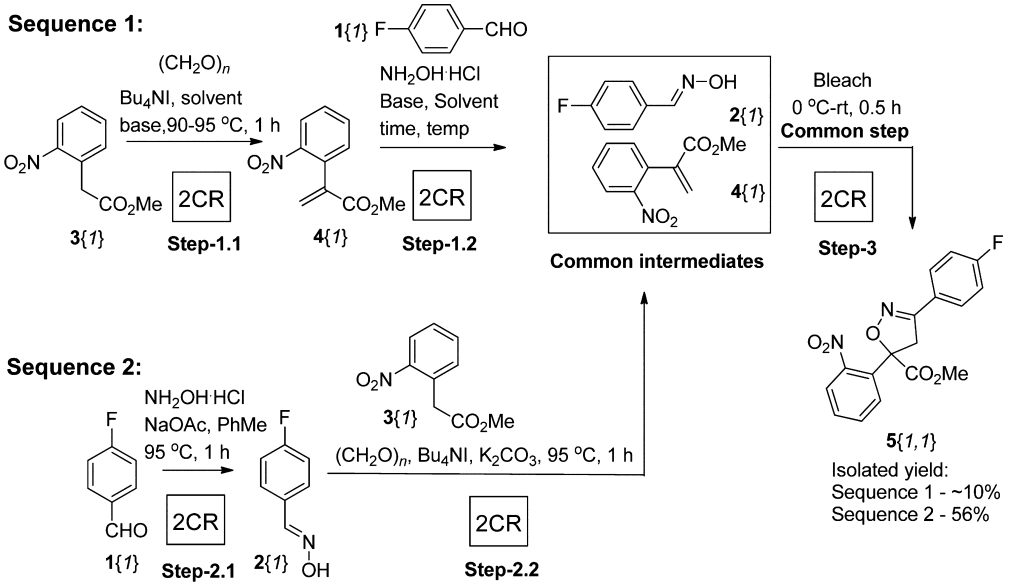
Scheme 2. Optimization of Reaction Sequences for the Synthesis of Methyl 3-(4-Fluorophenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (5{*1,1*}) by a One-Pot Multicomponent (2·2·2-Component) Reaction



Optimization of Step-1.1

Base (equiv)	Solvent	% Yield[a]
NaOAc (3.0)	PhMe	<30
DABCO (3.0)	PhMe	<30
$^{i}Pr_2NEt$ (3.0)	PhMe	NR[b]
$(CH_2NH_2)_2$ (3.0)	PhMe	NR
NEt_3 (3.0)	PhMe	NR
K_2CO_3 (3.0)	PhMe	~90
K_2CO_3 (1.5)	PhMe	~90
K_2CO_3 (1.5)	PhMe:EtOH (1:1)	~50
K_2CO_3 (1.5)	EtOH	<30

Optimization of Step-1.2

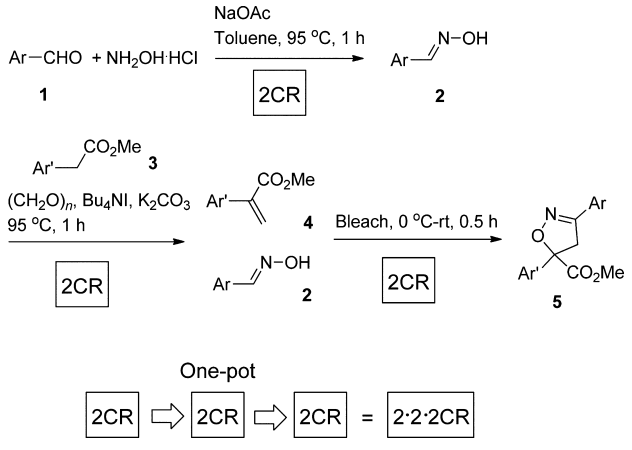
Base[c]	Solvent	Temp (°C)	Time (h)	% Yield[a]
NaOAc	PhMe: EtOH (1:1)	80	2	70
NaOAc	PhMe: EtOH (2:1)	80	2	65
NaOAc	PhMe: EtOH (3:1)	80	2	65
NaOAc	PhMe: EtOH (4:1)	80	2	70
K_2CO_3	PhMe: EtOH (4:1)	80	2	40
NaOAc	PhMe	80	2	90
NaOAc	PhMe	95	1	90
K_2CO_3	PhMe	95	2	60

all 2-CR sequences. However, the combination of four reactants in a one-pot fashion can lead to undesired side-product formation and, consequently, lower or no isoxazoline yield. Thereby, selection of the right sequence of addition, choice of solvent, base, and additive would hold key to the success of this transformation.

Our initial attempts centered on synthesizing the methyl 2-(2-nitrophenyl)acrylate first followed by the addition of 4-fluorobenzaldehyde and hydroxyl amine in the same pot to generate the oxime. The 1,3-dipolar cycloaddition reaction could then be performed by addition of bleach to generate the nitrile oxide in situ.

The oximes are normally synthesized in polar protic solvents in presence of an inorganic or an organic base.[17] The synthesis of 2-phenylacrylates generally uses K_2CO_3 as a base in presence of a phase-transfer catalyst and some of the commonly used solvents are DMF, DMF–H_2O, and toluene.[18] We thus tried various combinations of EtOH, DMF, and H_2O for the one-pot methodology. In the first step, methyl 2-(2-nitrophenyl)acrylate 4{*1*} was synthesized and 4-fluorobenzaldehyde 1{*1*} and hydroxyl amine were added to the same pot after cooling the reaction to rt (Scheme 2, sequence 1). The oxime 2{*1*} was formed by heating the resulting mixture. In the final step, the nitrile oxide was generated in situ by addition of bleach to the chilled reaction mixture of oxime 2{*1*} (and alkene 4{*1*}) to accomplish the 1,3-dipolar cycloaddition reaction. However, the

Scheme 3. Optimized Conditions for Methyl 3,5-Diaryl-Isoxazoline-5-carboxylate Synthesis by a One-pot Multicomponent (2·2·2-Component) Reaction



presence of desired isoxazoline 5{*1,1*} could not be identified by LCMS of the reaction mixture. We reasoned that the solvent and the choice of base played a role in this one-pot multicomponent transformation. Next, we used toluene/EtOH as the solvent mixture of choice. Though, satisfactory alkene 4{*1*} formation was observed by LCMS, only a trace amount of

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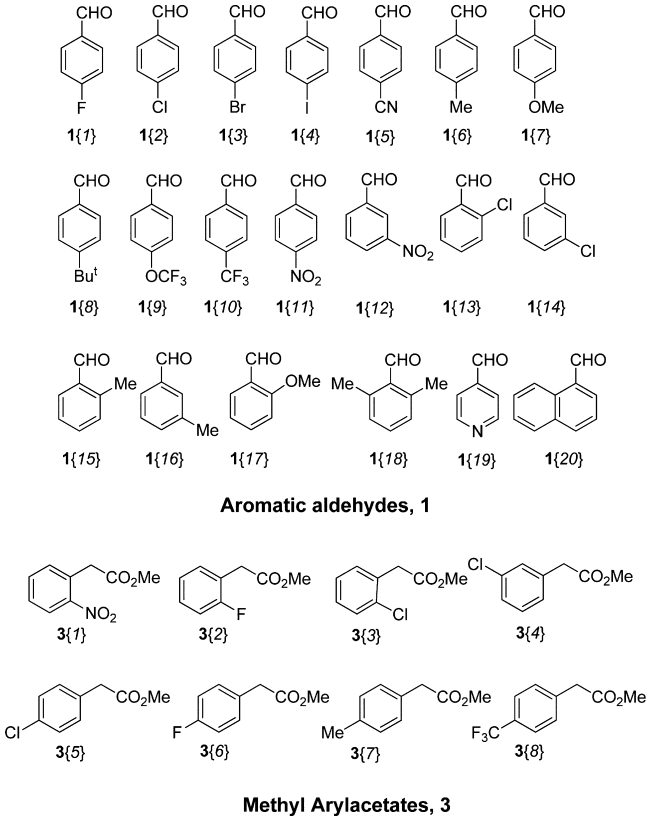

Figure 1. Variations on aromatic aldehydes (**1**) and methyl arylacetates (**3**) used.

product was seen by LCMS at the end of the completed sequence.

To identify the most suitable reaction condition, we further studied the individual steps as seen in Scheme 2 (table for optimization of step-1.1). Toluene as the solvent was found to result the best isolated yield for both the steps. However, a small amount of product **5**{*1,1*} (~10% isolated yield) was obtained by using toluene as the only solvent (with 3 equiv of K_2CO_3 without any further addition of base). Though it was possible to isolate the desired isoxazolines, the yield was still unsatisfactory and formation of undesired side products was observed. Similar results were obtained with other methyl 2-arylacetates and aldehydes. On further probing, methyl 2-arylacrylate **4** was found to be undergoing decomposition under the reaction conditions.

As a next step, we evaluated the effect of reversal of the sequence of the reactions (Scheme 2, sequence 2). 4-Fluorobenzaldehyde oxime **2**{*1*} was synthesized first followed by the addition of methyl 2-(2-nitrophenyl)acetate and paraformaldehyde to form methyl 2-(2-nitrophenyl)acrylate **4**{*1*}. The K_2CO_3 loading was reduced to ~1.5 equiv by using NaOAc as a base in the first step (oxime **2**{*1*} formation, Scheme 2, table for optimization of step-1.2). The final step was performed by adding bleach to this reaction mixture as before without any further modification. Interestingly, the corresponding isoxazoline **5**{*1,1*} was obtained in 56% isolated yield after purification by preparative HPLC.

The general scheme for this multicomponent synthesis is shown in Scheme 3. To expand the scope of this method, a diverse array of reactants was chosen (Figure 1). A total of

Table 1. Library of Methyl 3,5-Diaryl-isoxazoline-5-carboxylates

entry	aldehyde, (**1**)	methyl arylacetate (**3**)	methyl 3,5-diaryl-isoxazoline-5-carboxylate (**5**)	yield (%)
1	{*1*}	{*1*}	**5**{*1,1*}	56
2	{*1*}	{*2*}	**5**{*1,2*}	42
3	{*1*}	{*3*}	**5**{*1,3*}	40
4	{*1*}	{*4*}	**5**{*1,4*}	42
5	{*1*}	{*5*}	**5**{*1,5*}	60
6	{*1*}	{*6*}	**5**{*1,6*}	44
7	{*1*}	{*7*}	**5**{*1,7*}	50
8	{*1*}	{*8*}	**5**{*1,8*}	40
9	{*2*}	{*1*}	**5**{*2,1*}	53
10	{*2*}	{*2*}	**5**{*2,2*}	41
11	{*2*}	{*3*}	**5**{*2,3*}	38
12	{*2*}	{*4*}	**5**{*2,4*}	42
13	{*2*}	{*5*}	**5**{*2,5*}	50
14	{*2*}	{*6*}	**5**{*2,6*}	42
15	{*2*}	{*7*}	**5**{*2,7*}	42
16	{*2*}	{*8*}	**5**{*2,8*}	45
17	{*3*}	{*1*}	**5**{*3,1*}	45
18	{*3*}	{*2*}	**5**{*3,2*}	38
19	{*3*}	{*3*}	**5**{*3,3*}	36
20	{*3*}	{*4*}	**5**{*3,4*}	35
21	{*3*}	{*5*}	**5**{*3,5*}	45
22	{*3*}	{*6*}	**5**{*3,6*}	40
23	{*3*}	{*7*}	**5**{*3,7*}	38
24	{*3*}	{*8*}	**5**{*3,8*}	42
25	{*4*}	{*1*}	**5**{*4,1*}	30
26	{*4*}	{*2*}	**5**{*4,2*}	35
27	{*4*}	{*3*}	**5**{*4,3*}	32
28	{*4*}	{*4*}	**5**{*4,4*}	32
29	{*4*}	{*5*}	**5**{*4,5*}	39
30	{*4*}	{*6*}	**5**{*4,6*}	38
31	{*4*}	{*7*}	**5**{*4,7*}	36
32	{*4*}	{*8*}	**5**{*4,8*}	38
33	{*5*}	{*1*}	**5**{*5,1*}	45
34	{*5*}	{*2*}	**5**{*5,2*}	40
35	{*5*}	{*3*}	**5**{*5,3*}	45
36	{*5*}	{*4*}	**5**{*5,4*}	47
37	{*5*}	{*5*}	**5**{*5,5*}	48
38	{*5*}	{*6*}	**5**{*5,6*}	44
39	{*5*}	{*7*}	**5**{*5,7*}	45
40	{*5*}	{*8*}	**5**{*5,8*}	48
41	{*6*}	{*1*}	**5**{*6,1*}	51
42	{*6*}	{*2*}	**5**{*6,2*}	43
43	{*6*}	{*3*}	**5**{*6,3*}	47
44	{*6*}	{*4*}	**5**{*6,4*}	49
45	{*6*}	{*5*}	**5**{*6,5*}	60
46	{*6*}	{*6*}	**5**{*6,6*}	44
47	{*6*}	{*7*}	**5**{*6,7*}	50
48	{*6*}	{*8*}	**5**{*6,8*}	42
49	{*7*}	{*1*}	**5**{*7,1*}	52
50	{*7*}	{*2*}	**5**{*7,2*}	45
51	{*7*}	{*3*}	**5**{*7,3*}	45
52	{*7*}	{*4*}	**5**{*7,4*}	50
53	{*7*}	{*5*}	**5**{*7,5*}	52
54	{*7*}	{*6*}	**5**{*7,6*}	45
55	{*7*}	{*7*}	**5**{*7,7*}	51
56	{*7*}	{*8*}	**5**{*7,8*}	45

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Table 1. continued

entry	aldehyde, (**1**)	methyl arylacetate (**3**)	methyl 3,5-diaryl-isoxazoline-5-carboxylate (**5**)	yield (%)
57	{*8*}	{*1*}	**5**{*8,1*}	58
58	{*8*}	{*2*}	**5**{*8,2*}	40
59	{*8*}	{*3*}	**5**{*8,3*}	38
60	{*8*}	{*4*}	**5**{*8,4*}	55
61	{*8*}	{*5*}	**5**{*8,5*}	66
62	{*8*}	{*6*}	**5**{*8,6*}	42
63	{*8*}	{*7*}	**5**{*8,7*}	52
64	{*8*}	{*8*}	**5**{*8,8*}	55
65	{*9*}	{*1*}	**5**{*9,1*}	41
66	{*9*}	{*2*}	**5**{*9,2*}	49
67	{*9*}	{*3*}	**5**{*9,3*}	50
68	{*9*}	{*4*}	**5**{*9,4*}	50
69	{*9*}	{*5*}	**5**{*9,5*}	55
70	{*9*}	{*6*}	**5**{*9,6*}	50
71	{*9*}	{*7*}	**5**{*9,7*}	49
72	{*9*}	{*8*}	**5**{*9,8*}	50
73	{*10*}	{*1*}	**5**{*10,1*}	40
74	{*10*}	{*2*}	**5**{*10,2*}	45
75	{*10*}	{*3*}	**5**{*10,3*}	40
76	{*10*}	{*4*}	**5**{*10,4*}	48
77	{*10*}	{*5*}	**5**{*10,5*}	45
78	{*10*}	{*6*}	**5**{*10,6*}	48
79	{*10*}	{*7*}	**5**{*10,7*}	47
80	{*10*}	{*8*}	**5**{*10,8*}	45
81	{*11*}	{*1*}	**5**{*11,1*}	33
82	{*11*}	{*2*}	**5**{*11,2*}	48
83	{*11*}	{*3*}	**5**{*11,3*}	37
84	{*11*}	{*4*}	**5**{*11,4*}	35
85	{*11*}	{*5*}	**5**{*11,5*}	40
86	{*11*}	{*6*}	**5**{*11,6*}	45
87	{*11*}	{*7*}	**5**{*11,7*}	44
88	{*11*}	{*8*}	**5**{*11,8*}	42
89	{*12*}	{*1*}	**5**{*12,1*}	45
90	{*12*}	{*2*}	**5**{*12,2*}	52
91	{*12*}	{*3*}	**5**{*12,3*}	41
92	{*12*}	{*4*}	**5**{*12,4*}	40
93	{*12*}	{*5*}	**5**{*12,5*}	44
94	{*12*}	{*6*}	**5**{*12,6*}	49
95	{*12*}	{*7*}	**5**{*12,7*}	50
96	{*12*}	{*8*}	**5**{*12,8*}	45
97	{*13*}	{*1*}	**5**{*13,1*}	41
98	{*13*}	{*2*}	**5**{*13,2*}	48
99	{*13*}	{*3*}	**5**{*13,3*}	40
100	{*13*}	{*4*}	**5**{*13,4*}	38
101	{*13*}	{*5*}	**5**{*13,5*}	45
102	{*13*}	{*6*}	**5**{*13,6*}	45
103	{*13*}	{*7*}	**5**{*13,7*}	42
104	{*13*}	{*8*}	**5**{*13,8*}	39
105	{*14*}	{*1*}	**5**{*14,1*}	47
106	{*14*}	{*2*}	**5**{*14,2*}	51
107	{*14*}	{*3*}	**5**{*14,3*}	44
108	{*14*}	{*4*}	**5**{*14,4*}	40
109	{*14*}	{*5*}	**5**{*14,5*}	47
110	{*14*}	{*6*}	**5**{*14,6*}	48
111	{*14*}	{*7*}	**5**{*14,7*}	44
112	{*14*}	{*8*}	**5**{*14,8*}	43
113	{*15*}	{*1*}	**5**{*15,1*}	34
114	{*15*}	{*2*}	**5**{*15,2*}	36
115	{*15*}	{*3*}	**5**{*15,3*}	34
116	{*15*}	{*4*}	**5**{*15,4*}	38
117	{*15*}	{*5*}	**5**{*15,5*}	52
118	{*15*}	{*6*}	**5**{*15,6*}	40
119	{*15*}	{*7*}	**5**{*15,7*}	42
120	{*15*}	{*8*}	**5**{*15,8*}	38
121	{*16*}	{*1*}	**5**{*16,1*}	50
122	{*16*}	{*2*}	**5**{*16,2*}	43
123	{*16*}	{*3*}	**5**{*16,3*}	42
124	{*16*}	{*4*}	**5**{*16,4*}	45
125	{*16*}	{*5*}	**5**{*16,5*}	58
126	{*16*}	{*6*}	**5**{*16,6*}	45
127	{*16*}	{*7*}	**5**{*16,7*}	44
128	{*16*}	{*8*}	**5**{*16,8*}	42
129	{*17*}	{*1*}	**5**{*17,1*}	45
130	{*17*}	{*2*}	**5**{*17,2*}	44
131	{*17*}	{*3*}	**5**{*17,3*}	48
132	{*17*}	{*4*}	**5**{*17,4*}	44
133	{*17*}	{*5*}	**5**{*17,5*}	50
134	{*17*}	{*6*}	**5**{*17,6*}	42
135	{*17*}	{*7*}	**5**{*17,7*}	42
136	{*17*}	{*8*}	**5**{*17,8*}	42
137	{*18*}	{*1*}	**5**{*18,1*}	43
138	{*18*}	{*2*}	**5**{*18,2*}	48
139	{*18*}	{*3*}	**5**{*18,3*}	48
140	{*18*}	{*4*}	**5**{*18,4*}	50
141	{*18*}	{*5*}	**5**{*18,5*}	52
142	{*18*}	{*6*}	**5**{*18,6*}	48
143	{*18*}	{*7*}	**5**{*18,7*}	52
144	{*18*}	{*8*}	**5**{*18,8*}	45
145	{*19*}	{*1*}	**5**{*19,1*}	40
146	{*19*}	{*2*}	**5**{*19,2*}	48
147	{*19*}	{*3*}	**5**{*19,3*}	42
148	{*19*}	{*4*}	**5**{*19,4*}	45
149	{*19*}	{*5*}	**5**{*19,5*}	52
150	{*19*}	{*6*}	**5**{*19,6*}	44
151	{*19*}	{*7*}	**5**{*19,7*}	40
152	{*19*}	{*8*}	**5**{*19,8*}	40
153	{*20*}	{*1*}	**5**{*20,1*}	45
154	{*20*}	{*2*}	**5**{*20,2*}	48
155	{*20*}	{*3*}	**5**{*20,3*}	43
156	{*20*}	{*4*}	**5**{*20,4*}	40
157	{*20*}	{*5*}	**5**{*20,5*}	48
158	{*20*}	{*6*}	**5**{*20,6*}	45
159	{*20*}	{*7*}	**5**{*20,7*}	38
160	{*20*}	{*8*}	**5**{*20,8*}	38

18 benzaldehydes were used. There was no significant effect on conversion with both electron donating and electron withdrawing substitution on the aryl ring. The o-, m-, or p-substitution did not have any effect on the yield as well. The reaction was successful with isonicotinaldehyde (**19**{*1*}) and 1-naphthaldehyde (**20**{*1*}) with yields comparable to the benzaldehydes. The robustness of this HT synthesis was also established by using 8 methyl arylacetates. Under the present reaction conditions, a variety of substituents were found to be tolerated well. The isolated yields were found to be in the range of 30−66% after purification of the crude products by preparative HPLC (Table 1). Molecular weights ranged from 297 to 476 as a result of functional group diversity.

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In conclusion, we have successfully synthesized a 160-membered library of methyl 3,5-diaryl-isoxazoline-5-carboxylates. By suitable selection of the reaction sequence, the synthesis could be achieved in one-pot through sequential 2-CR steps. This 2·2·2-CR variant of otherwise very common synthesis methodology was unexplored before. A wide range of functional groups was tolerated and the compounds were obtained in satisfactory overall yields and purity suitable for biological activity screening.

EXPERIMENTAL PROCEDURES

General Procedure for the One-Pot Reaction. A mixture of aromatic aldehyde (0.5 mmol), hydroxylamine hydrochloride (0.6 mmol), and NaOAc (0.9 mmol) in toluene (2 mL) was stirred at 95 °C for 1 h. The reaction mixture was cooled to room temperature followed by the addition of the ester (0.6 mmol), paraformaldehyde (1.7 mmol), potassium carbonate (0.8 mmol), and tetrabutylammonium iodide (0.06 mmol) to the same reaction pot and was heated at 95 °C for 1 h. The reaction mixture was then cooled to 0 °C, and bleach (5 mL) was added under vigorous stirring. It was then stirred at room temperature for an additional 0.5 h and allowed to settle. The organic layer was separated and the residual aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was passed through a plug of anhyd Na_2SO_4 and concentrated in a centrifugal evaporator (Genevac HT-4X) to give the desired crude product. This was purified by preparative HPLC (column Xbridge Prep C18, 19 × 250 mm; mobile phase 5 mM $(NH_4)_2CO_3$/MeCN, 70:10−30:90; flow rate 12 mL/min; run time 10−20 min).

Methyl 3-(4-Fluorophenyl)-4,5-dihydro-5-(2-nitrophenyl)isoxazole-5-carboxylate (5{*1,1*}). Isolated yield: 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8.24 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.65−7.69 (m, 2H), 7.57 (t, J = 8.4 Hz, 1H), 7.09 (t, J = 8.8 Hz, 2H), 4.78 (d, J = 17.6 Hz, 1H), 3.76 (s, 3H), 3.43 (d, J = 17.6 Hz, 1H). UPLC-MS (M^+ + H): 345.01, 91% purity.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra and UPLC-MS data of 45 representative compounds. ^{1}H and ^{13}C NMR and UPLC-MS traces of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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