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Multicomponent Synthesis of 3-Heteroarylpropionic Acids

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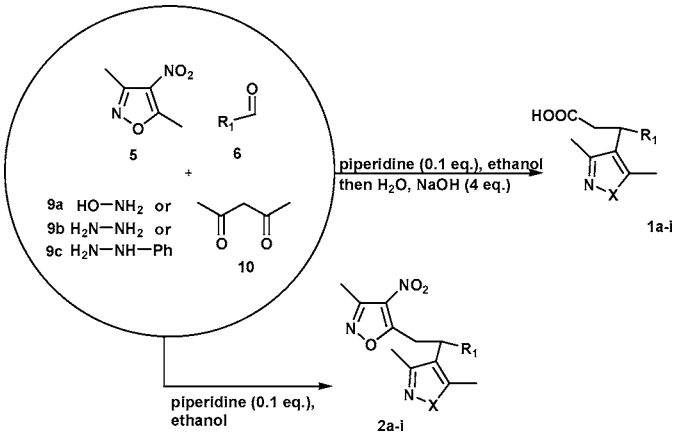
ABSTRACT



A four component one-pot procedure (4-MC) was developed to assemble 3-heteroarylpropionic acids from commercially available materials. This new methodology affords the title compounds in high yields and without the use of chromatography.

Recently, 3-aryl and 3-heteroarylpropionic acids have been found to possess several biological activities.[1−3] Some 3-arylpropionic acids were found to be selective agonists of the sphingosine-1-phospate receptor.[1] Other members of this class have been patented as antinflammatory agents[2] or for treatment of insulin resistance.[3] As a part of our ongoing efforts in developing multicomponent one-pot procedures using commercially available materials,[4−6] we envisaged a novel modular synthesis leading to 3-heteroarylpropionic acids **1** and 4-nitroisoxazol-5-ethanyl compounds **2**, some of which were reported to have antimicrobial activity[7] (Figure 1).

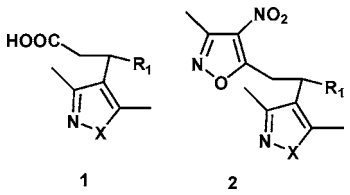


Figure 1. Target compounds: 3-heteroarylpropionic acids **1** and 4-nitroisoxazol-5-ethanyl compounds **2**.

Additionally, the diaryl methine motif in **1** and **2** is present in a number of drugs and natural products.[8] A retrosynthetic

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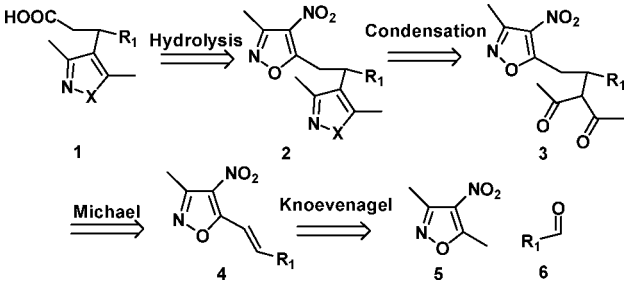
analysis of targets **1** and **2** showed that 3,5-dimethyl-4-nitroisoxazole **5** could serve as a starting material for a sequence of anionic driven reactions (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Targets **1** and **2**



We have recently reported a one-pot procedure by which adducts **3** (Scheme 1) were obtained in high yields from commercially available isoxazole **5**, an aromatic aldehyde **6** and acetylacetone **10**.[4] We reasoned that compound **2** could be prepared using an extension of this procedure that included the addition of hydroxylamine, hydrazine, or a substituted hydrazine. Finally, we planned to prepare 3-arylpropionic acids **1** by hydrolysis of the 3-methyl-4-nitroisoxazol-5-yl group present in **2**. The hydrolysis of the 3-methyl-4-nitroisoxazol-5-yl core to a carboxylate is a well-documented process,[9,10] and although the mechanistic details of this reaction have been clarified, its synthetic utility has not been addressed. From the synthetic standpoint, the 3,5-dimethyl-4-nitroisoxazol-5-yl core could be considered a masked carboxylate that is revealed upon hydrolysis. Therefore, the 3,5-dimethyl-4-nitroisoxazolate **7** is formally equivalent to an acetic acid dianion **8** (Figure 2).

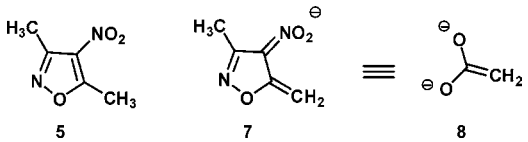
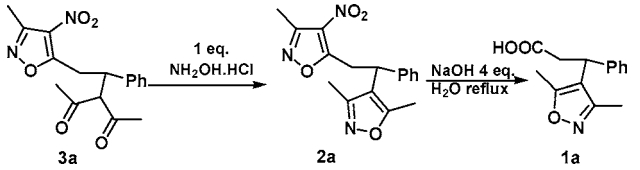


Figure 2. 3,5-Dimethyl-4-nitroisoxazolate **7** and acetic acid dianion **8**.

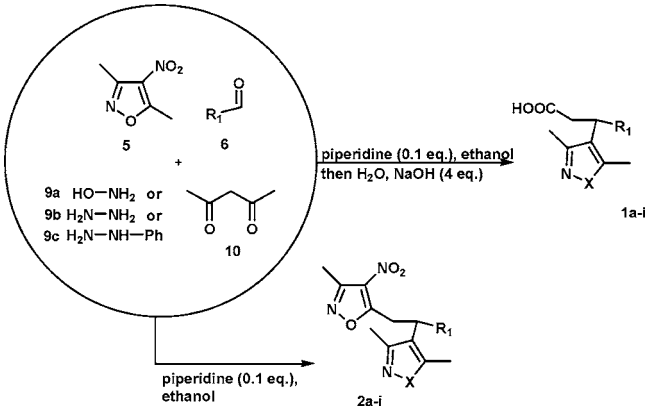
We first carried out a stepwise synthesis of compounds **2a** and **1a** using hydroxylamine **9a** as the nucleophile, in order to determine an optimal set of reaction conditions (Scheme 2). We were delighted to observe that 1 equiv of **9a** was enough to produce **2a** in good yield and that **2a** was

Scheme 2. Synthesis of Compounds **2a** and **1a**



obtained in similar yield by reacting together **5**, **6**, **10**, and **9a** in a one-pot process (Scheme 3). We then studied the conversion of **2a** to acid **1a**. The best results were obtained with mixtures of ethanol/water as the solvent and a minimum of 4 equiv of sodium hydroxide. We also established a protocol for the purification of **1a** and **2a** that did not involve the intervention of chromatography. Compound **2a** was purified by crystallization, whereas compound **1a** was obtained pure by mean of an base/acid extraction.

Scheme 3. One-Pot Synthesis of 3-Heteroarylpropionic Acids **1a**−**i** and 4-Nitroisoxazol-5-ethanyl Compounds **2a**−**i**



With a set of experimental conditions in hand, we focused our attention on a study of the dinucleophile component. Indeed, β-diketones have been extensively used to generate heterocycles when reacted with opportune dinucleophiles.[11] Compound **3a** (Scheme 2) reacted well with hydroxylamine **9a**, hydrazine **9b**, and phenyl-hydrazine **9c**. However, the reaction of **3a** with benzamidine, acetamidine, and methyl 3-aminocronate gave only starting material. Having determined an appropriate set of reagents and conditions, we carried out the synthesis of compounds **1a**−**i** in a one-pot fashion (Scheme 3, Table 1).

Typically **5** (3 mmol) and an aromatic aldehyde **6** (3 mmol) were reacted in the presence of piperidine (0.1 equiv) in ethanol (10 mL) at 60 °C for 1 h and then acetylacetone **10** (1.5 equiv) was added. The reaction mixture was stirred at 60 °C for 6 h, then **9a**−**c** (1 equiv) was added, and the reaction mixture stirred at 60 °C for another 7 h. At this point water (10 mL) and NaOH (4 equiv) were added, and the reaction refluxed for 6 h.

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Table 1. One-Pot Synthesis of Compounds **1a**−**i**

entry	compd	R_1	X	yield, %[a]
1	**1a**	Ph	O	88
2	**1b**	Ph	NH	85
3	**1c**	Ph	N-Ph	61
4	**1d**	*p*-Cl-Ph	O	80
5	**1e**	*p*-Cl-Ph	NH	95
6	**1f**	*p*-Cl-Ph	N-Ph	72
7	**1g**	2,4-Cl-Ph	O	85
8	**1h**	2,4-Cl-Ph	NH	69
9	**1i**	2,4-Cl- Ph	N-Ph	74

[a] Isolated yields after acid/base extraction.

Table 2. One-Pot Synthesis of Compounds **2a**−**i**

entry	compd	R_1	X	yield, %[a]
1	**2a**	Ph	O	90
2	**2b**	Ph	NH	48
3	**2c**	Ph	N-Ph	85
4	**2d**	*p*-Cl-Ph	O	65
5	**2e**	*p*-Cl-Ph	NH	59
6	**2f**	*p*-Cl-Ph	N-Ph	65
7	**2g**	2,4-Cl-Ph	O	84
8	**2h**	2,4-Cl-Ph	NH	61
9	**2i**	2,4-Cl-Ph	N-Ph	86

[a] Isolated yields after cristallisation.

The brown oil obtained was concentrated en vacuo and washed with chloroform. The water layer was then made acidic with dilute HCl, and the product was extracted from the water layer into chloroform. As the acid products were isolated by a simple extraction method, the need for chromatography was obviated. Polyheterocyclic compounds **2a**−**i** were obtained in high yield by omitting the hydrolysis step (aq base, Δ) (Scheme 3, Table 2). This ease of purification complements the one-pot procedures, making these methodologies facile, practical, and rapid to execute.

In conclusion, we reported two 4-MC one-pot procedures to prepare two families of products with potential medicinal properties using inexpensive and commercially available materials. These syntheses are modular and benefit from a simple method of purification that does not require chromatography. Both families of compounds are highly functionalized and could serve as valuable intermediates for the generation of diverse classes of compounds.

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Supporting Information Available: General experimental, general one-pot procedure for the preparation of compounds **1a**−**i** (Table 1) and for compounds **2a**−**i** (Table 2), spectroscopic data of compounds **1a**−**i** and **2a**−**i**, and ^{1}H NMR spectra of compounds **1a**−**i** and **2a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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