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Novel Synthetic Approach to 6,7-Dihydro-5*H*-imidazo[1,5-a]-pyrazin-8-ones

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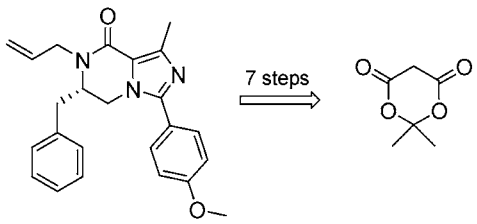
ABSTRACT



A novel route to highly substituted chiral 6,7-dihydro-5*H*-imidazo[1,5-a]pyrazine-8-ones starting from Meldrum's acid is disclosed. The key features of the methodology are the incorporation of amino esters as a chiral pool and facile mild intramolecular cyclization to form the pyrazine ring. Incorporation of various substituents at different stages of the synthesis from various building block sets makes this methodology readily amenable to parallel synthesis.

Imidazopyrazines **1** are structural units found in numerous bioactive natural products, drugs, and drug candidates. They are well represented in the area of medicinal chemistry, acting on a number of targets including the CRF receptor,[1] GABAA receptor,[2] melanocortin receptor,[3] etc. Recently, 6,7-dihydro-5*H*-imidazo[1,5-a]pyrazin-8-ones **2** were disclosed as Factor Xa inhibitors[4] (Figure 1).

The imidazo[1,5-a]pyrazine heterocyclic system is one of the less known members of the azaindolizine family. Reported synthetic methods involve either the formation of the imidazole ring[5] or the much lesser known routes of formation of the pyrazine ring[6] by ring closure onto an existing imidazole intermediate. A recent report by Trcek et al.[7] describes a one-pot approach to the imidazo[1,5-a]-pyrazine system based on the cyclocondensation of 3-[(2-amino-1,2-dicyanoethen-1-yl)amino]-2-(benzylamino)-propenoates with ortho esters. However, these methods do not provide an easy entry to 6,7-dihydro-5*H*-imidazo[1,5-a]-pyrazine-8-ones of interest. This partially saturated system opens the avenue to build chirality into the molecule and introduce much desired diversity points for generation of

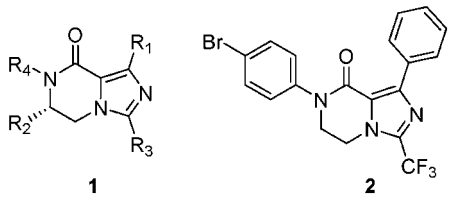


Figure 1.

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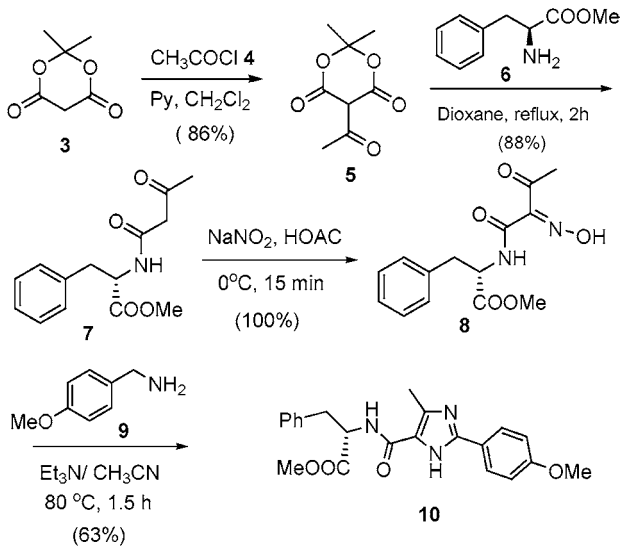
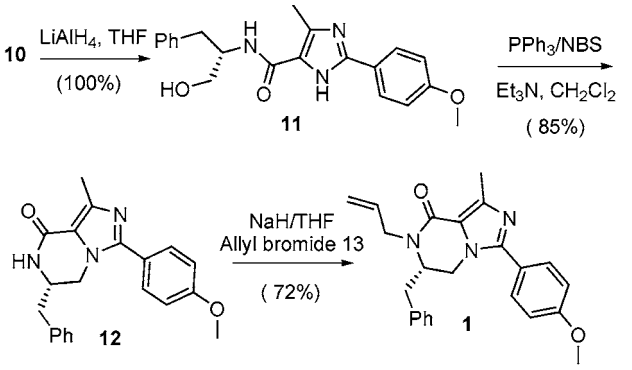
Scheme 1. Synthesis of Imidazole Intermediate **10**



Scheme 2. Synthesis of 6,7-Dihydro-5*H*-imidazo[1,5-a]pyrazine-8-ones **1**



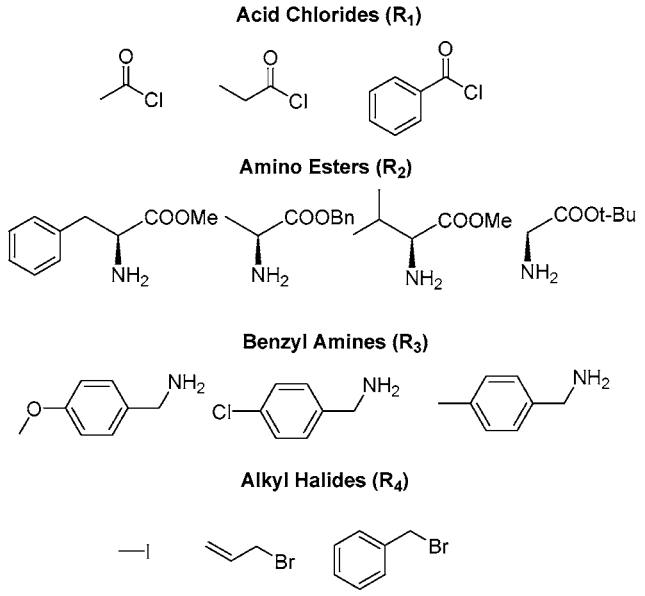


Figure 2. Building Blocks for Parallel Synthesis.

combinatorial arrays. Our approach to this heterocyclic system conveniently makes use of amino esters as the chiral component and involves intramolecular cyclization to form the pyrazine ring as detailed below.

Our approach to synthesizing a common imidazole intermediate starts with Meldrum's acid (Scheme 1). Thus, reaction of Meldrum's acid **3** with acetyl chloride[8] afforded **5**, which was treated with α-amino esters such as phenylalanine methyl ester **6** to give the *β*-ketoamide **7**. Conversion to the hydroxyimine **8** was quantitative using sodium nitrite[9] in acetic acid. Reaction of **8** with 4-methoxybenzylamine **9** gave the cyclized imidazole[10] intermediate **10**.

Initial attempts to cyclize the imidazole ester intermediate **10** under basic conditions afforded the desired product pyrazine-5,8-dione, but the product was found to be unstable under acidic or basic conditions. However, the intermediate **10** underwent smooth selective reduction of the ester upon treatment with $LiAlH_4$ to give the alcohol **11** in quantitative yield. Reduction worked equally well when benzyl or *tert*-butyl esters were used in the place of methyl ester. In situ conversion of the alcohol **11** to the corresponding primary bromide[11] and further cyclization to form the pyrazine ring **12** could be carried out in one pot and was found to be very facile under the mild conditions employed. Further alkylation of the amide afforded the substituted dihydroimidazopyrazine **1** (Scheme 2). The heterocycle **1** was found to be stable through a range of pH values and could be isolated in good purity.

Application of this method for parallel solution-phase synthesis[12] was demonstrated by generating a small library of compounds varying the four substituents R_1-R_4 in compound **1**. The building blocks chosen to introduce the diversity in these positions are shown in Figure 2.

All the building blocks employed gave good yields, except for the phenyl substituent in the R_1 position, which gave lower yields (~20−58%, depending on the R_3 employed) for the imidazole formation step (**8** to **10**), probably due to steric hindrance during cyclization. Ester reduction and final ring closure to form the pyrazine ring worked well with all the amino esters, including the sterically hindered valine methyl ester (Table 1). The enantiomeric purity of representative compounds with the chiral

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(12) (a) Solution-phase parallel synthesis was carried out in 8 mL vials using J-Kem blocks with heating and cooling capabilities. (b) All compounds were purified by HPLC. A Gilson HPLC instrument with Unipoint software was used. Column: Phenomenex C18 Luna 21.6 × 60 mm, 5 μM. Solvent A: water (0.02% TFA buffer). Solvent B: acetonitrile (0.02% TFA buffer). Solvent gradient: time 0 min (5% B), 2.5 min (5% B), 12 min (95% B), hold 3 min (95% B). Flow rate: 22.5 mL/min. Detection: 215 and 254 nm. Reported yields are isolated yields.

Table 1. Formation of Pyrazine Ring **12**

R_1	R_2	R_3	yield **10** to **12** (%)
methyl	benzyl	4-methoxyphenyl	85
methyl	benzyl	4-chlorophenyl	46
methyl	benzyl	4-methylphenyl	58
ethyl	benzyl	4-methoxyphenyl	56
ethyl	benzyl	4-chlorophenyl	57
ethyl	benzyl	4-methylphenyl	67
Phenyl	benzyl	4-methoxyphenyl	61
phenyl	benzyl	4-chlorophenyl	40
phenyl	benzyl	4-methylphenyl	54
methyl	*i*-propyl	4-methoxyphenyl	63
methyl	methyl	4-chlorophenyl	80
methyl	H	4-methylphenyl	85

amino acids used was determined by NMR measurements using (*S*)-(+)-α-(trifluoromethyl)benzyl alcohol and/or europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. The compounds were found to be of high chiral purity without racemization during the synthetic transformations.

In summary, we have developed a novel route for the 6,7-dihydro-5*H*-imidazo[1,5-a]pyrazine-8-one system involving mild reaction conditions and limited purification. The method is amenable for parallel synthesis, providing multiple sites for diversification leading up to highly substituted chiral imidazopyrazines of biological significance.

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Supporting Information Available: Experimental procedures and ^{1}H NMR and LC/MS data for intermediates and final products of chemistry validation and LC/MS data for the parallel synthesis array. This material is available free of charge via the Internet at http://pubs.acs.org.

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