



Iodine catalyzed mild 4CR protocol for synthesis of Tetrahydroimidazo[1,2-*a*]pyridines: cascade construction of multiple C–C and C–Hetero bonds



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Dedicated to Dr. Abdolali Alizadeh in appreciation of all lessons I have learned from him.

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ABSTRACT

A highly convergent and straight forward synthesis of N-fused heterocycles, including 1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acids is successfully achieved via a one-pot four-component cascade reaction utilizing pyruvic acid, aldehydes, diamines and 1,1-bis(methylthio)-2-nitroethylene (BMTNE) in the presence of a catalytic amount of molecular iodine in acetonitrile. The new efficient domino protocol generates two rings by the concomitant formation of C–N (three) and C–C (two) multiple bonds presumably involving a sequence of *N,N*-acetal formation, Knoevenagel reaction, *aza*–ene reaction, imine–enamine/keto–enol tautomerization, and *N*-cyclization as key steps. The merit of this protocol is highlighted by its easily available and economical starting materials, operational simplicity, efficient utilization of all the reactants, clean reaction profile, simple workup procedure, and tolerance of a wide variety of functional groups.

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1. Introduction

The central theme of organic synthesis is the construction and cleavage of bonds in organic molecules. Modern synthesis involves the design of efficient synthetic protocol that minimizes the number of synthetic steps for the rapid generation of functionalized molecules with interesting properties. One approach to achieve this goal involves the development of eco-compatible, multicomponent procedures. Multicomponent reactions (MCRs) offer a wide range of possibilities for the construction of pre-defined highly complex molecules in a single step with high atom economy, minimum time, labor, cost, and straight forward experimental procedures.¹ These benefits are highlights for multicomponent cascade reactions, which involve in situ production of an intermediate with a strategic reactive site for subsequent transformations.² In the past decade, a lot of multicomponent reactions have been reported,^{3,4} yet developing novel MCRs that meet almost all of advantages above is still in the burgeoning phase.

In recent times, the use of molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the

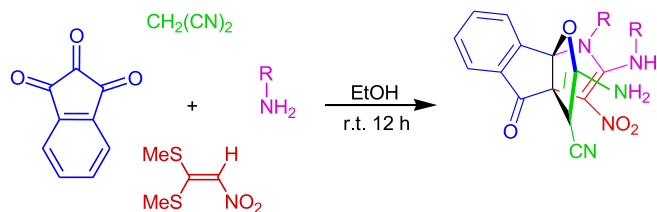
corresponding products in excellent yields with high selectivity.⁵ The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations.⁶ So the development of a reaction that uses catalytic amounts of non toxic and readily available iodine should greatly contribute to the creation of environmentally benign processes. Interestingly, to some extent, the reactions promoted by iodine usually afford unexpected results.⁷

Nitro ketene amins (NKA) and related compounds possessing the conjugated system N=C=EWG are important versatile synthetic intermediates in synthetic chemistry and they have received increasing attention recently.⁸ Their usage for constructing a variety of nitrogen containing heterocycles or fused heterocyclic compounds that are hardly accessible by other synthetic methods has been extensively studied.⁹ The notable feature of NKA is the highly polarized ethylene systems with electro-donating amino group and electro-withdrawing substituent at both ends. This unique structural feature makes them serve as bis-nucleophiles reacting with various bis-electrophiles.

Our research goal during the past few years has been the synthesis of a library of pharmacologically relevant fused

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polyheterocyclic systems employing enamines and amins.¹⁰ Recently, we have become interested in the application of nitro ketene amination intermediates resulting from the reaction of 1,1-bis(methylthio)-2-nitroethylene (BMTNE) and diamines or primary amines for the synthesis of interesting heterocycles in one-pot processes. During a previous investigation, we succeeded in developing a novel class of oxa-aza[3.3.3]propellane fused derivatives based on reaction of NKA and Knoevenagel adduct from ninhydrin and malonitrile (Scheme 1).^{10b}



Scheme 1. Synthesis of fused oxa-aza[3.3.3]propellanes via one-pot, four-component reaction.

2. Results and discussion

Encouraged by this successful effort, I decided to perform the reaction of heterocyclic ketene amination (HKAs) and the Knoevenagel adduct generated in situ from pyruvic acid and benzaldehyde, to evaluate the construction of useful fused azaheterocycle molecules under mild reaction conditions. Reactions of pyruvic acid derivatives with bisnucleophiles have been applied for the synthesis of various types of heterocycles since the beginning of the last century. On the other hand, multicomponent reactions of pyruvic acid leading to heterocycles have rarely been investigated.

During the course of our studies, molecular iodine was discovered, which can be applied as a good catalyst for the activation of the carbonyl group of benzaldehyde¹¹ and the iodine catalyzed Michael reactions are well known.¹² Accordingly, at first, the reaction of pyruvic acid and 4-chlorobenzaldehyde under different conditions was evaluated that afforded the expected Knoevenagel adduct intermediate. Initially, the reaction was carried out in ethanol at room temperature. Whether the catalyst was added or not, the target compound **4a** was not obtained after 24 h (Table 1, entries 1 and 2). However, when the reaction was heated at reflux and the molecular iodine was added, I found that the reaction was complete and the desirable Knoevenagel adduct was obtained in an isolated yield of 27% within 24 h (Table 1, entry 3). Subsequently, reaction conditions was optimized by screening several solvents, and of those examined, acetonitrile was the most suitable. With molecular iodine as good promoter in hand, next I intended to optimize its loading, and it was found that the use of 10 mol % of I₂ provided the best result. Reducing the mol % of I₂ in the reaction increased the reaction time and lowered the yield, and increasing the catalyst loading did not show any improvement (Table 1, entries

6 and 7). Therefore, the best reaction conditions were achieved by employing with molecular iodine (0.1 mmol) in acetonitrile under reflux for 2 h (Table 1, entry 8).

Next, to verify the possibility to perform a 'classic' one-pot four-component reaction, the reaction was carried out by sequential addition of reagents ethylenediamine, nitro ketene dithioacetal (BMTNE), pyruvic acid and 4-chlorobenzaldehyde in one flask under the same reaction conditions. This manner avoids the isolation of the intermediates and should save time of execution and solvent amounts, and afford better yields. Thus, in a pilot reaction, ethylenediamine and BMTNE in acetonitrile, was combined. The resultant reaction mixture was stirred to complete the SN reaction as monitored by thin-layer chromatography (TLC). After the formation of HKA **5**, pyruvic acid and 4-chlorobenzaldehyde with catalytic amount of I₂ (10 mol %) were introduced and the reaction was heated at reflux in an oil bath until completion (monitored by TLC). The desired product was isolated, filtered, and washed with cold ethanol to afford the pure product **4a**. The resultant pure compound was identified on the basis of spectroscopic data. Because of the existence of two stereogenic centers in the products **4d–f**, mixture of two diastereomers was expected. For **4d** and **4f** products, two diastereomers were formed (Fig. 1). But, the ¹H and ¹³C NMR spectral data of **4e** clearly indicated that only one of the two possible diastereomers was obtained for this product.

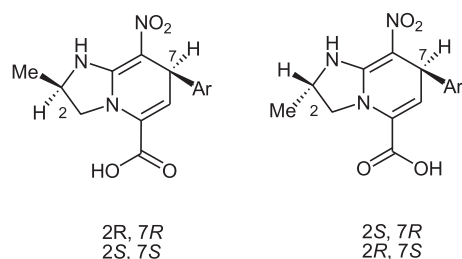


Fig. 1. Expected mixture of two diastereomers of **4d–f**.

With the optimal reaction conditions, we then investigated the use of different starting materials in order to determine the reactivity domain of the cascade reaction (Table 2). For ethylenediamines and aromatic aldehydes **2**, the substituents, whether with electron-withdrawing, or electron-releasing groups on the aromatic ring, afforded corresponding products in excellent yields. Application of other diamines such as 1,3-propylenediamines and 1,4-butanediamine lead to a complex mixture, which was difficult to purify and characterize (Table 2).

The molecular structure of products **4a–f** was elucidated from elemental analysis, IR, and ¹H NMR and ¹³C NMR spectra. The mass spectrum of **4b** displayed the molecular ion peak at *m/z* 301, which is in agreement with the proposed structure. The IR spectrum of this compound showed an absorption band due to the NH stretching frequency at 3352 cm⁻¹. Absorption bands at 1727, 1651 cm⁻¹ are due to the C=O and NC=C groups stretching frequencies. The ¹H NMR spectrum of **4b** showed one sharp singlet for the methyl group ($\delta=2.23$ ppm), three multiplets for two CH₂ groups, because these protons are diastereotopic ($\delta=3.68–3.74$, 4.06–4.16 and 4.24–4.32 ppm), two doublets for CH groups ($\delta=4.80$ and 6.06 ppm, ³J_{HH}=5.6 Hz), and two singlets for NH and OH groups ($\delta=9.32$ and 13.17 ppm). Also, four aromatic hydrogens gave rise to characteristic signals in the aromatic region of the spectrum. Observation of 13 distinct signals in the ¹H-decoupled ¹³C NMR spectrum of **4b** is in agreement with the proposed structure. The most important region of the spectrum is related to resonances due to, CNO₂, CCO and CO, which appear at $\delta=119.0$, 127.0 and 163.2 ppm.

Table 1

Screening optimum reaction conditions for the formation of intermediate Knoevenagel condensation product

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Yield ^a %
1	—	EtOH	rt	24	nr ^b
2	—	EtOH	rt	24	nr
3	I ₂ (10)	EtOH	70	24	27
4	I ₂ (10)	MeOH	65	24	14
5	I ₂ (10)	THF	70	10	30
6	I ₂ (5)	MeCN	80	5	44
7	I ₂ (20)	MeCN	80	2	92
8	I ₂ (10)	MeCN	80	2	94

^a Isolated yield.

^b No reaction.

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