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Formal aza-[3+3] versus aza-[3+2] cycloadditions of heterocyclic enaminones with maleic anhydride and maleimides: skeletally diverse synthesis of pyrrolizidinones, indolizidinones, and pyrroloazepinones

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ABSTRACT

The domino aza-annulation of cyclic enaminones with maleic anhydride and maleimides was investigated, and selectively one-step skeletally diverse synthesis of each alkaloid-like pyrrolizidinone, indolizidinone, and pyrrolo[1,2-*a*]azepinone was developed, switching between aza-[3+3] and aza-[3+2] modes of formal cycloaddition reactions. For the synthesis of pyrroloazepinones, seven-membered enaminone and maleic anhydride or maleimides are efficient, via the [3+2] mode. To access indolizidinones, five or six-membered enaminones are the choice, and both [3+2] and [3+3] modes were viable exclusively with maleic anhydride. Pyrrolizidinone can be selectively synthesized in good yield through the [3+2] mode, only with five-membered enaminone and *N*-(4-NO_2Ph)maleimide, under catalysis by PTSA.

1. Introduction

Fused bicyclic heterocycles with a bridgehead nitrogen atom are present in various natural and unnatural bioactive compounds. Among these heterocycles, 1-azabicyclo[3.3.0]octanes,[1] 1-azabicyclo[4.3.0]nonanes,[2] and 1-azabicyclo[5.3.0]decanes[3] have been synthesized by diverse approaches because they occur in pyrrolizidines, indolizidines, and pyrroloazepines, which are three important classes of structural scaffolds present in alkaloids and alkaloid analogues with application in medicinal chemistry.[4]

Maleic anhydride and maleimides are easily available and versatile electrophiles whose use in the synthesis of *N*-heterocycles, including 1-azabicycles, is well described.[5,6] A particular synthetic approach involves their direct reaction with an enaminone.[7–18] However, a close analysis of the reactions depicted in Fig. 1 reveals a complex chameleonic behavior of enaminones in the aza-

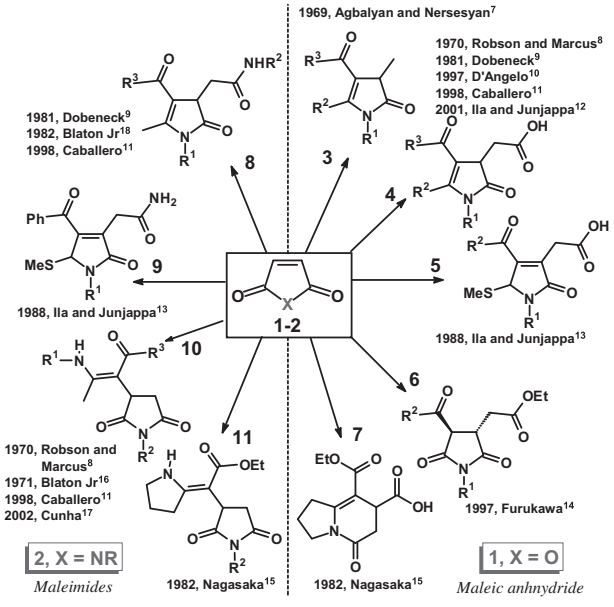

Fig. 1. Reaction of enaminones with maleic anhydride and maleimides.

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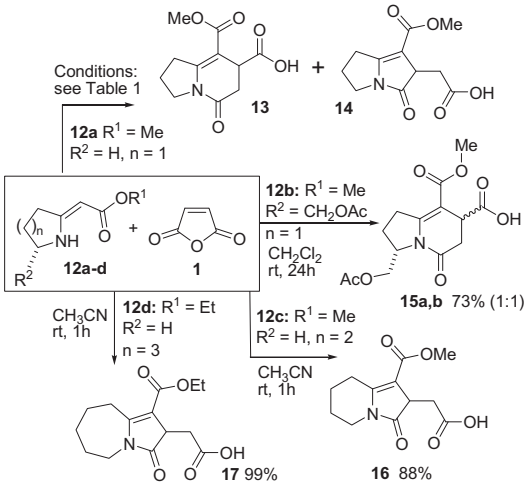
annulations with the studied electrophiles, whereby small variation of the nature of substituents of both enaminone and mentioned electrophiles, may result in significant variation of the double bond position, and in nature of the obtained heterocycle. The 2-pyrrolidone nucleus present in compounds **3**–**5** and **8**,**9**, generated through formal aza-[3+2] cycloaddition, predominated in most of these reactions. The Michael adduct **10** and **11** were observed only in reactions with maleimides, and 3,4-*trans*-disubstituted succinimide **6** was formed only with maleic anhydride, Fig. 1.

The formation of product **7** is remarkable; while acyclic enaminones are prone to react with maleic anhydride through formal [3+2] cycloaddition, the five-membered enaminone provides the indolizidinone **7**, which corresponds to a formal aza-[3+3] cycloaddition. This is the unique example, and somewhat not expected, of such reaction patterns.[15]

Despite the scenario depicted in Fig. 1 represents a significant contribution in the development of concise synthesis of *N*-based heterocycles,[19] the synthetic potential of the formal aza-cycloaddition reactions of heterocyclic enaminones with maleic anhydride/maleimides in the synthesis of densely substituted 1-azabicycles is still under-exploited. Inspired by these facts, we decided to develop a simple and divergent approach adequate to the purpose of synthesize such heterocycles in a quick way, with emphasis on skeletal diversity.[20] This strategy is in connection with our effort devoted to the development of simple one-pot and/or multicomponent synthetic methodologies, which permit direct access of compounds to biological evaluation.[21] One of such approach employs enaminones[22] as building blocks for the synthesis of *N*-heterocycles through formal aza-cycloaddition reactions.[17,23] In this way, we disclosure herein our ongoing study concerning the formal aza-[3+2] and formal aza-[3+3] cycloaddition reactions of cyclic enaminones,[24] including a chiral one, with maleic anhydride and *N*-aryl-maleimides, wherein pyrrolizidinone, indolizidinone, and pyrroloazepinone heterocycles could be selectively obtained.

2. Results and discussion

To gain insight into the synthetic and mechanistic implications in the reactions of maleic anhydride and maleimides with heterocyclic enaminones en route to azabicycles, five, six, and seven-membered enaminone derivatives **12a**–**d** were prepared, including a chiral one.[25] In an initial trial, enaminone **12a** was reacted with maleic anhydride **1** in the condition described by Nagasaka and co-workers for the ethyl ester analogous of **12a**.[15] In this condition, we obtained indolizidinone **13** in good yield, in a mmol scale, Scheme 1 and Table 1 (entry 1).



Scheme 1. Reactions of cyclic enaminones with maleic anhydride.

Table 1
Reaction conditions to the formal aza-cycloaddition of enaminone **12a** and maleic anhydride **1**

Entry[a]	Solvent	Catalyst (mol %)	Yield (%) **13**	**14**
1	Benzene	—	78	—
2	CH_2Cl_2	—	85	—
3	$CHCl_3$	—	15	10
4	CH_3CN	—	85	—
5[b]	CH_3CN	—	81	16
6[c]	CH_3CN	BiI_3 (10)	61	19
7	CH_3CN	BiI_3 (100)	50	36

[a] Reaction carried out 0.1 M in each reagent at rt.
[b] Reaction at reflux.
[c] Reaction carried out 0.6 M using 100 mmol of each reagent at rt.

Formation of the six-membered ring instead of five one, i.e., indolizidinone **13** versus pyrrolizidinone **14** (corresponding to formal aza[3+3] instead of aza[3+2] cycloaddition) with the five-membered enaminone **12a** is not well understood, because in all described reactions of acyclic enaminones with maleic anhydride the 2-pyrrolidone nucleus is formed.[7–13]

We rationalized that a solvent effect should be operating in the competition between the formal aza-[3+3] versus aza-[3+2] cycloadditions, because the reactions shown in Fig. 1 with acyclic enaminones were performed in polar solvents, while Nagasaka employed benzene. In this way, we reevaluated the reaction of **12a** with **1** in polar solvents. After some experimentation, we discovered that in CH_2Cl_2 and CH_3CN the same indolizidinone **13** was obtained in yields slightly better than in benzene as solvent (Table 1, entries 2 and 4). Curiously, using $CHCl_3$ as solvent, indolizidinone **13** was obtained together with the isomeric pyrrolizidinone **14** (entry 3), as well as when the reaction was carried out in CH_3CN at reflux (entry 5). Despite **14** being formed in low yield, this aza-[3+2] product was not previously observed in the aza-annulation described by Nagasaka.[15]

Our synthetic enrollment with bismuth salts as Lewis acids in organic synthesis[21] prompted us to use bismuth iodine in CH_3CN, which increased the amount of isolated aza[3+2] product **14** (entries 6 and 7), being this the best condition to the one-pot synthesis of the pyrrolizidinone **14**. However, the formal aza[3+3] product **13** was always formed as the major or exclusive compound in all conditions herein studied with five-membered enaminone **12a** and maleic anhydride. This was also the result in the reaction of chiral cyclic enaminone **12b**, which allowed isolation of inseparable mixture of epimeric indolizidinones **15a**,**b** in good yield, Scheme 1.

The structure of pyrrolizidinone **14** was elucidated based on the spectral analysis. Moreover, during the synthetic methodology development, a single crystal of **14** was obtained and its solid state structure was unambiguously assigned to gain insight into conformational bias and intramolecular and intermolecular interactions, Fig. 2.

Distinction between indolizidinone **13** and isomeric pyrrolizidinone **14** could be easily done through analyses of their ^{1}H NMR data of the moiety corresponding to the atoms from maleic anhydride, Fig. 3. Thus, the endocyclic conformationally restricted $COCH_2CHCO_2H$ spin system of **13** appears as an AMX system, while the equivalent moiety $COCHCH_2CO_2H$ of **14** is an ABX one. Besides, the multiplicities of CH_2 in **13** are two double doublet (2.61 and 2.87 ppm), and the methynic hydrogen is a large double doublet (3.78 ppm). In the pyrrolizidinone **14**, the free rotation of exocyclic α methylene results in almost the same ^3J value to the coupling constant of the two hydrogen of CH_2 with vicinal CH, and then each hydrogen CH_2 of **14** appears as double doublets (3.00 and