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Heterocycles from Morita–Baylis–Hillman adducts: synthesis of 5-oxopyrazolidines, arylidene-5-oxopyrazolidines, and oxo-2,5-dihydro-pyrazols

José Tiago M. Correia [a], Manoel T. Rodrigues, Jr. [a], Hugo Santos [a], Cláudio F. Tormena [b], Fernando Coelho [a,*]

[a] Laboratory of Synthesis of Natural Products and Drugs, University of Campinas, Institute of Chemistry, 13083-970 Campinas, SP, Brazil
[b] Laboratory of Physical Organic Chemistry, University of Campinas, Institute of Chemistry, 13083-970 Campinas, SP, Brazil

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ABSTRACT

Starting from Morita–Baylis–Hillman (MBH) adducts, an approach for the synthesis of oxopyrazolidines, arylidene-oxopyrazolidines, and oxo-2,5-dihydropyrazoles is described. The method is based on a tandem process involving a Michael addition of amino-guanidine into silylated and acetylated MBH adducts, followed by intramolecular cyclization. The use of acetylated MBH adducts led also to the synthesis of unusual pyrazoles, which is facilitated by an unexpected base-mediated equilibrium.

1. Introduction

Heterocycles form the most basic building blocks of life playing also a key role in several segments of the chemical industry. They are also important monomers for polymers and moieties of biologically active compounds, such as agrochemicals and drugs.[1] A large amount of additives and modifiers used in different segments of chemical industry, such as cosmetics, reprographic, plastics, and information storage are also heterocyclic in their constitution.[1c] Owing to the vast commercial and biological relevance of heterocycles in organic chemistry, many methodologies are available for their preparation.[1a,b]

Pyrazolones and pyrazolidinones are common heterocycles with a great diversity of biological properties.[2] For instance, they exhibited analgesic, antibacterial, and antifungal activities (**1** and **2**, Fig. 1),[3] as well as anti-tumoral activity[4] and anti-ischemic effect.[5] Recently, pyrazolones **3** and **4** (Fig. 1) were identified as HIV-integrase inhibitors, which constitutes a new class of antiretroviral agents.[6]

The synthetic utility and biological activity of pyrazolidinones have also raised interest on these compounds in the last decade.[7] They have been used as templates in enantioselective Diels–Alder,[8] Michael,[9] and click reactions.[10] Pyrazolidinones are also present in some bicyclic antibiotics developed by Eli Lilly (Fig. 1, compounds **5**, **6**, and **7**) some years ago.[11]

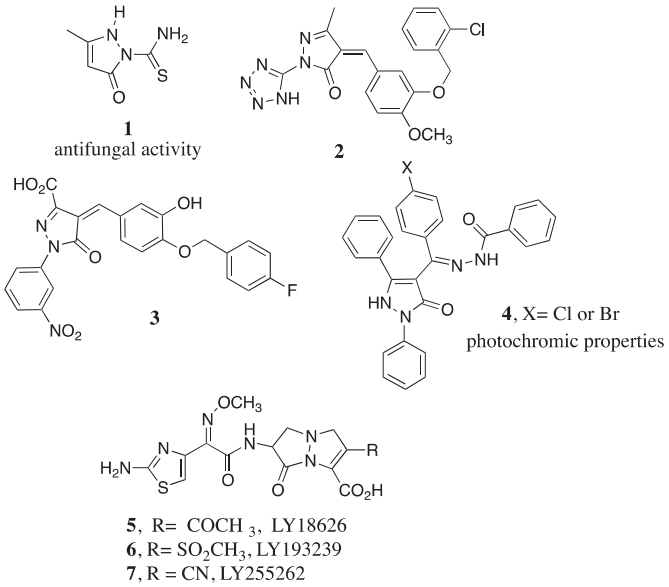

Fig. 1. Some representative examples of biologically active pyrazolones and pyrazolidinones.

* Corresponding author. Tel.: +55 19 3521 3085; fax: +55 19 3521 3023; e-mail address: coelho@iqm.unicamp.br (F. Coelho).

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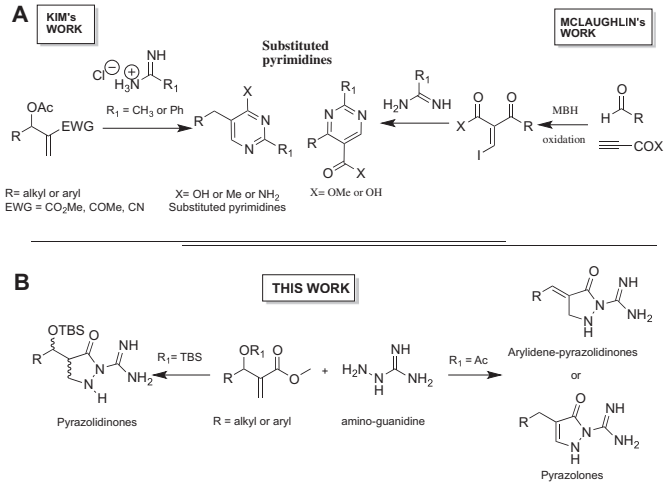
The presence of both pyrazolone and pyrazolidinone units in many molecules of pharmaceutical interest has also led to the development of a great variety of methods for their preparation.

The most classic approach to prepare pyrazolones is via the reaction between a β-ketoester, a β-cyanoester or α,β-unsaturated esters and hydrazine or hydrazine derivatives (alkyl, aryl or heterocyclic).[12] Recently, Ma et al.[13] reported on a one-pot synthesis of arylidene-pyrazolones by treatment of a mixture of ethyl acetoacetate, electrodeficient phenyl-hydrazines and electron poor aromatic aldehydes in the presence of microwaves. Alternatively, palladium can be used as catalyst for the preparation of pyrazolones from 1,2-diaza-1,3-butadienes.[14] Organocatalyzed methodologies for the synthesis of pyrazolones have also been reported recently.[15]

Most methods for the preparation of pyrazolidinones rely on [3+2] cycloadditions using dipoles, such as diazoalkanes,[16] nitrile imines,[17] azomethine[18] or hydrazones.[19] Metal-catalyzed amination of allenes is also used as an alternative methodology to obtain pyrazolidinones or pyrazolidines.[20] Recently, oxo-ketenes were used as substrate for [1,3]dipolar cycloaddition with hydrazones.[21] Addition of substituted hydrazines to α,β-unsaturated esters has also been used as approach to prepare pyrazolidinones.[19]

The Morita–Baylis–Hillman (MBH) reaction[22,23] is a versatile chemical transformation that provides small poly-functionalized molecules, which can be used as Michael acceptors in the preparation of a great diversity of molecules.[24]

Recently, Kim et al.[25] and McLaughlin et al.[26] have independently investigated the chemical behavior of MBH adducts as substrates for a reaction with amidine. These reactions gave the respective substituted pyrimidines or 2,5-substituted pyrimidine carboxylate as main products in good yields (Scheme 1).



Scheme 1. Kim's and McLaughlin's syntheses of substituted pyrimidines and our approach to the synthesis of pyrazolones and pyrazolidinones both from Morita–Baylis–Hillman adducts.

These results associated with our interest in preparing some pyrazolones and pyrazolidinones for biological screening against some strains of human cancer cells stimulated us to investigate the chemical behavior of amino-guanidine in the presence of silylated and acetylated MBH adducts. Curiously, guanidine has already been used as catalyst for the MBH reaction,[27] but this bis-nucleophile or their derivatives have never been investigated as reagent in a Michael addition with MBH adducts.

We have already demonstrated the influence of the silylated protecting groups in the diastereoselectivity of the Michael addition reaction on MBH adducts.[28] If this behavior is also observed here, it would be possible to control the relative stereochemistries of two stereogenic centers and form a new five-membered ring in a single step (Scheme 1, part B).

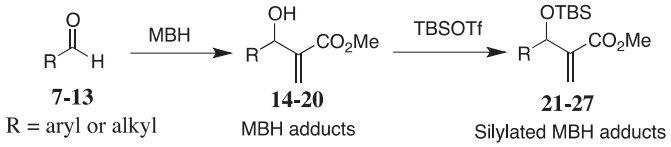
We therefore disclose herein a new, simple, and direct approach to the synthesis of pyrazolones and pyrazolidinones from MBH adducts. Our methodology uses a one-pot two step sequence involving a Michael addition of amino-guanidine, followed by intramolecular cyclization.

2. Results and discussion

The investigation was initiated by preparing some MBH adducts according to a method we described some years ago.[29] The adducts were then silylated in the presence of TBSOTf/NEt_3 to provide the corresponding silyl ethers in good to excellent overall yields (Table 1).

The silylated compounds were then diluted in MeOH and treated, under reflux, with aminoguanidine carbonate in the presence of triethylamine to give the substituted pyrazolidinones in good yields and diastereoselectivity varying from 2:1 to 7:1 after 3 h (Table 2).

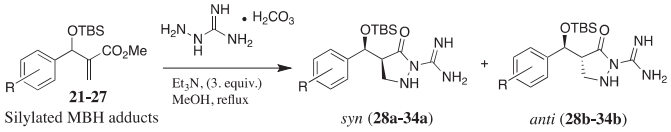
Table 1
MBH reaction and silylation



Entry	Aldehyde	MBH, yield (%)[a,b]	Silylation (%)[b]
1	R=4-NO_2Ph (**7**)	**14**, 97	**21**, 97
2	R=2-F–Ph (**8**)	**15**, 87	**22**, 94
3	R=3-Cl–Ph (**9**)	**16**, 91	**23**, >99
4	R=4-Cl–Ph (**10**)	**17**, 87	**24**, >99
5	R=4-*t*Bu–Ph (**11**)	**18**, 77	**25**, >99
6	R=4-MeO-Ph (**12**)	**19**, 72	**26**, >99
9	R=3,4-OCH_2O–Ph (**13**)	**20**, 73	**27**, >99

[a] The reactions were carried out using an excess of methyl acrylate (as solvent) and 0.65 equiv of DABCO at room temperature or in the presence of ultrasound radiation.
[b] Yields refer to isolated and purified products.

Table 2
Michael addition reaction with amino-guanidine



Entry	Silylated adduct	Yield (%)[a]	*syn*: *anti* ratio[b, c]
1	**21**, R=4-NO_2	**28a**/**b**, 83	2:1
2	**22**, R=2-F	**29a**/**b**, 81	7:1
3	**23**, R=3-Cl	**30a**/**b**, 78	5:1
4	**24**, R=4-Cl	**31a**/**b**, 88	4:1
5	**25**, R=4-*t*Bu	**32a**/**b**, 83	3:1
6	**26**, R=4-MeO	**33a**/**b**, 81	5:1
9	**27**, R=3,4-OCH_2–	**34a**/**b**, 83	2:1

[a] Yields refer to isolated and purified products.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] The relative stereochemistry was determined by measuring the coupling constant of the duplet attributed to the carbinolic hydrogen.

A wide range of MBH adducts are well tolerated, allowing the synthesis of a set of substituted pyrazolidinones in a tandem sequence. For all reactions, diastereoselectivity favored the *syn* diastereoisomers. These results are in accordance with previous observations made by us[28] and confirmed elsewhere.[30] Unfortunately, all chromatographic attempts to separate the diastereoisomers failed.