Synthesis of Substituted Pyrazolones from Morita-Baylis-Hillman Adducts

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INTRODUCTION

The pyrazolone moiety has been gaining attention because of its biological importance. This structure is present in some useful analgesic, antipyretic and anti-inflammatory drugs, namely metamizole, phenazone, propyphenazone and ampyrone[1].
Therefore, we have focused our attention in the synthesis of this class of molecules using the classical 1,3-dicarbonyl compounds approach, which were obtained from Morita-Baylis-Hillman adducts.

RESULTS AND DISCUSSION

The synthesis of the 2,3-dihydro-1*H*-pyrazol-3-one derivatives was accomplished in four steps starting from the commercial aldehydes **1-4**. The first step consists of a Morita-Baylis-Hillman reaction of the aldehydes with methyl acrylate catalyzed by DABCO, using the reaction conditions previously optimized by our group[2]. The MBH adducts **5-8** were then oxidized using IBX[3], and were directly reduced used a borane dimethylsulfide complex (**Scheme 1**). As seen in **Table 1**, the yields for the 2-steps, after chromatographic purification of the product, varied from 65-91%. After that, hydrazine hydrate is added to a solution of the *β*-keto esters **9-12** in methanol with a catalytic amount of acetic acid, and after an overnight period, the solvent is evaporated, ethyl acetate added, and the product is filtered off, giving only the 4-methyl-2,3-dihydro-1*H*-pyrazol-3-ones **13-16** in good yields (70-100%).

Scheme 1. Oxidation-reduction path to the pyrazolones.

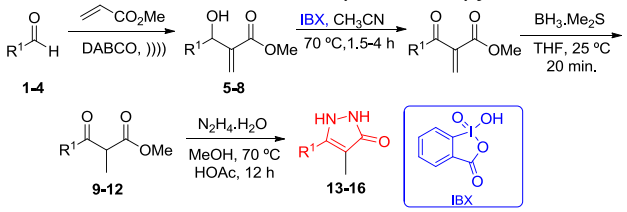

Table 1. Pyrazolone synthesis from the MBH adducts.

Entry	MBH (%)[a]	*β*-keto ester (%)[a,b]	Pyrazolone (%)[a]
1	**5** $R^1 = C_6H_5$ (74)	**9** (80)	**13** (70)
2	**6** R^1 = 3-ClC_6H_4 (85)	**10** (68)	**14** (78)
3	**7** R^1 = 4-MeOC_6H_4 (70)	**11** (91)	**15** (74)
4	**8** R^1 = 4-$O_2NC_6H_4$ (96)	**12** (65)	**16** (100)

[a] Yields refer to isolated and purified products. [b] Two-step yield.

The MBH **8**, **19** and **20** adducts were also used as substrates for an intermolecular Heck reaction[4] catalyzed by a Najera oxime-derived palladacycle and 4-iodophenol as aryl halide (**Scheme 2**) giving the Heck adducts (HA) **21-23** in very good yields (85-96%, **Table 2**). Applying the same reaction conditions that were used for the *β*-keto esters, the 4-(4-hydroxybenzyl)-2,3-dihydro-1*H*-pyrazol-3-ones **24-26** were obtained in good yields (60-92%).

Scheme 2. Heck reaction path to the pyrazolones.

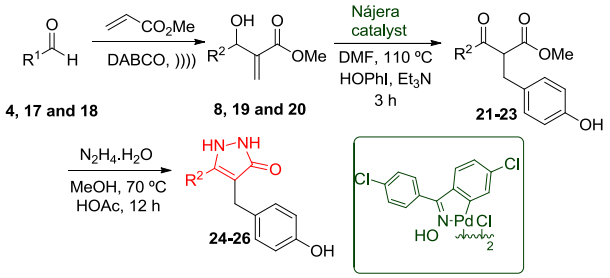

Table 2. Pyrazolone synthesis from the Heck adducts (HA).

Entry	MBH (%)[a]	HA (%)[a]	Pyrazolone (%)[a]
1	**8** R^1 = 4-$O_2NC_6H_4$ (96)	**21** (96)	**24** (74)
2	**19** R^1 = propyl (85)	**22** (85)	**25** (92)
3	**20** R^1 = 2-thienyl (85)	**23** (90)	**26** (60)

[a] Yields refer to isolated and purified products.

CONCLUSION

In summary, we have presented a useful approach towards the synthesis of *β*-keto esters from MBH adducts and by reacting those with hydrazine hydrate, generated substituted pyrazolones, in high yields.

ACKNOWLEDGEMENTS

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