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PII: S0040-4039(16)31301-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.10.008
Reference: TETL 48178

To appear in: *Tetrahedron Letters*

Received Date: 15 August 2016
Revised Date: 28 September 2016
Accepted Date: 2 October 2016

Please cite this article as: Siqueira, M.d.S., Silva-Filho, L.C.d., $NbCl_5$-promoted the synthesis of 4*H*-Pyrans through Multicomponent reaction, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.10.008

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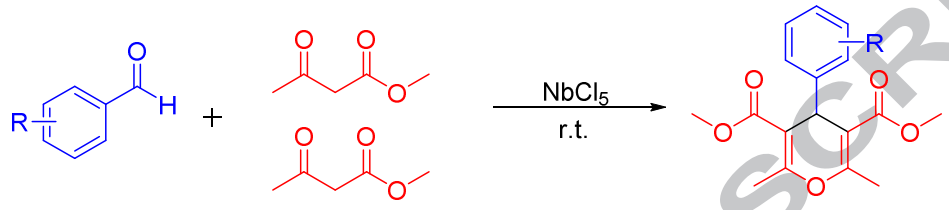

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$NbCl_5$-promoted the synthesis of 4*H*-Pyrans through Multicomponent reaction

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Niobium Pentachloride
Multicomponent reaction
Pyran derivatives
Lewis Acid

ABSTRACT

Multicomponent reactions between β-ketoesters and benzaldehydes for the synthesis of 4*H*-pyran derivatives promoted by Niobium Pentachloride ($NbCl_5$) were carried out, providing good yields and reasonable reaction times under mild reaction conditions.

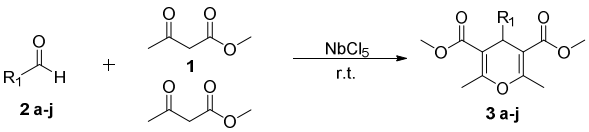
4*H*-pyran derivatives are an important class of natural organic compounds with several biological and pharmacological activities, such as anti-coagulant, spasmolytic, anticancer, antibacterial and antifungal, diuretic, specific IK_{Ca} channel blockers.[1] Different synthetic approaches have been reported in the literature for the synthesis of 4*H*-pyran derivatives, including the Michael addiction reaction in α,β-unsaturated dicarbonyl compounds followed by cyclization, [4 + 2] cycloaddition of enones and alkynes, and multicomponent reactions (MCRs) among aldehydes and different active methylene compounds.[2]

A multicomponent reaction is defined as any process in which three or more reactants react in one pot to form a product which contains portions of all the reactants, generating products with structural complexity in a single step.[3] The MCRs have the advantages of selectivity, synthetic convergence, and atom-economy.[4] Moreover, MCRs have the additional advantage of simplicity and synthetic efficiency emerging as an powerful tool in modern synthetic organic chemistry.[5]

The use of catalysts (metallic, acid or enzymatic) in the development of MCRs have also been subject of study in several research groups.[6] The catalysts can act by promoting the occurrence of reactions that do not occur without their presence, thus reducing reaction times, improving the reactions yield and, consequently, varying the ratio of the products formed. [6]

In the last two decades, there was an increasing interest from researchers in the use of niobium pentachloride ($NbCl_5$), a strong Lewis acid, in organic synthesis. Because its low cost and commercial availability, our group and other researchers used $NbCl_5$ as an effective catalyst in synthetic methodologies in several reactions.[7,8]

In this work, a new method for the synthesis of 4*H*-pyran derivatives by multicomponent reaction (MCR) between 2 equivalents of methyl acetoacetate (**1**) and benzaldehyde derivatives and heteroaromatic aldehydes (**2a-j**) promoted by niobium pentachloride, is described. (Scheme 1)



Scheme 1. MCR between methyl acetoacetate (**1**) and benzaldehyde derivatives and heteroaromatic aldehydes (**2 a-j**) promoted by $NbCl_5$.

Firstly, the multicomponent reaction between, methyl acetoacetate (**1**) (2.0 equiv.) and benzaldehyde (**2a**) (1.0 equiv.), in the presence of different concentrations (0.0, 0.1, 0.5 or 1.0 equiv.) of niobium pentachloride, was used as a model in order to develop a protocol for the optimization of the reaction conditions. The reaction was performed under N_2 atmosphere in anhydrous dichloromethane, at room temperature for 48, 72 or 96 hours. The product **3a** was isolated by column chromatography on silica gel and its structure was confirmed by ^1H NMR and ^{13}C NMR.[9] Results are summarized in Table 1.

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Table 1. Results obtained by MRC between methyl acetoacetate (**1**) and benzaldehyde (**2a**) varying the $NbCl_5$ concentration and reactional time.

entry	$NbCl_5$ (%)	Time (hours)	Yield (%)[a]
1	1.0	96	73
2	1.0	72	80
3	1.0	48	30
4	0.5	72	55
5	0.2	72	23
6	0.1	72	15
7	0.0	120	0

[a] Isolated Yields

Table 1 shows that the results obtained in the reactions with 0.0, 0.1 and 0.5 equivalents of $NbCl_5$ do not occur or show insignificant yields (entries 4-7 table 1). In 48 hours, using 1.0 equivalent of $NbCl_5$, it is possible to verify that the reaction is not completed (entry 3, table 1) due to a large quantity of intermediate, as seen by thin layer chromatography. At 96 hours, the product begins to be degraded, with a reduction in yield (entry 1, table 1). Based on these results, it was established a time of 72 hours and 1.0 equivalent in mol of $NbCl_5$ (entry 2, table 1) for the others reactions performed.

In an effort to obtain improved yields, various solvents were screened in the MCR of methyl acetoacetate and benzaldehyde at room temperature and the results are summarized in table 2. THF, dichloroethane and acetonitrile provided poor yields of 4*H*-pyran derivative. The reaction in EtOH and MeOH did not present the formation of product. These results proved that dichloromethane is a good choice as a solvent for the studied MCR.

Table 2. Results obtained to the MCR between methyl acetoacetate (**1**) and benzaldehyde (**2a**) in different solvents.[a]

Entry	Solvent	Yield[b] (%)
1	CH_3CN	55
2	THF	30
3	DCE	39
4	EtOH	0
5	MeOH	0

[a] Reaction conditions: methyl acetoacetate (2.0 mmol), benzaldehyde (1.0 mmol), $NbCl_5$ (1.0 mmol), room temperature, 72 h.
[b] Isolated yields.

Based on these results, it was established a time of 72 hours, using CH_2Cl_2 as solvent and 1.0 equivalent in mol of $NbCl_5$ (entry 2, table 1) for the others reactions performed.

After optimization of the reaction conditions, other aldehydes (**2 b–j**) were examined in the MCR for the synthesis of 4*H*-pyran derivatives in the presence of $NbCl_5$. (table 3)

Table 3. Results obtained by MRC between methyl acetoacetate (**1**) and benzaldehyde derivatives and heteroaromatic aldehydes (**2 a-j**) in the presence of $NbCl_5$.

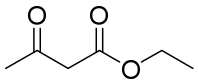
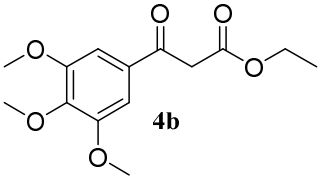
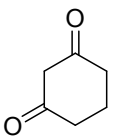
Aldehyde	R_1	Yield (%)[a]
2a	C_6H_5	80 (**3a**)
2b	4-(C_6H_5)-C_6H_4	91 (**3b**)
2c	4-(OH)-C_6H_4	78 (**3c**)
2d	4-(Br)-C_6H_4	76 (**3d**)
2e	4-(NO_2)-C_6H_4	77 (**3e**)
2f	4-(SCH_3)-C_6H_4	83 (**3f**)
2g	4-(CH_3)-C_6H_4	79 (**3g**)
2h	4-pyridyl	Traces (**3h**)
2i	2-thiophene	Traces (**3i**)
2j	2-furan	Traces (**3j**)

[a] Isolated Yields

The results in Table 2 show that by using 1.0 equivalent of $NbCl_5$ and a reaction time of 72 hours, it was possible to obtain 4*H*-pyran (**3 a-g**) derivatives with high yields (76-91%) under mild reaction conditions (room temperature). Large yield differences were not observed by changing the benzaldehyde derivative. For the heteroaromatic aldehydes **2h**, **2i** and **2j**, in the reaction conditions tested (1.0 equiv. of $NbCl_5$), was verified a high formation of polymerization products, making it impossible the purification of products.

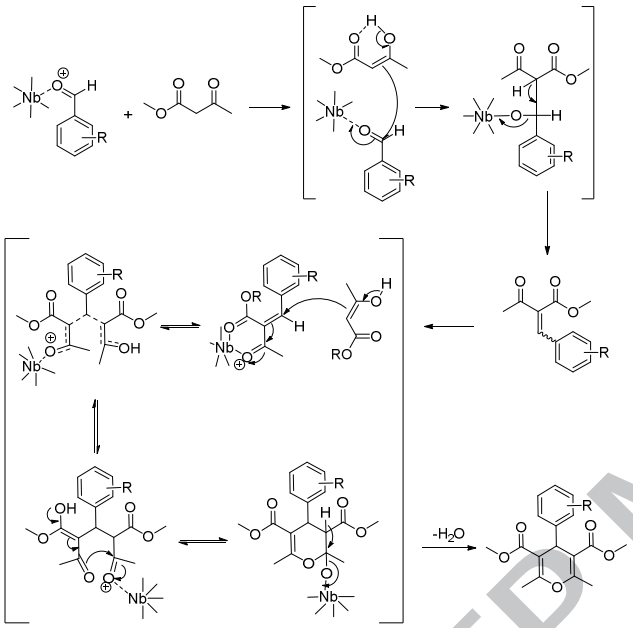
In addition, tests were performed by varying the 1,3-dicarbonyl derivatives used (**4a-c**) in the presence of benzaldehyde (**2a**) using 1.0 eq. of $NbCl_5$, CH_3CN as solvent in 72 hours (table 4). The compounds **4a** and **4c** provided products with high yield, but with the compound **4b** not was verified the formation of the product, probably, due to the high steric hindrance promoted by trimethoxyphenyl group.

Table 4. Results obtained by MRC test between 1,3-dicarbonyl derivatives (**4a-c**) and benzaldehyde (2**a**) in the presence of $NbCl_5$.

Aldehyde	1,3-dicarbonyl compound	Yield (%)[a]
2a	 **4a**	78 (**5a**)
2a	 **4b**	0 (**5b**)
2a	 **4c**	87 (**5c**)

[a] Isolated yields.

A mechanistic proposal for multicomponent reaction promoted by $NbCl_5$ is showed in Scheme 2. Probably, a Knoevenagel condensation reaction between the aldehyde derivative and methyl acetoacetate initially occurs, forming the benzylidene derivative *in situ*. The β-ketoester becomes prone to attack due to keto-enol tautomerism and the attack takes place on the carbon of the aldehyde, which is more electrophilic due to the complexation with the niobium pentachloride. The benzylidene derivative reacts with the second equivalent of methyl acetate through Michael addition reaction, followed by a closing ring reaction to obtain the 4*H*-pyran derivative.



Scheme 2. Mechanistic proposal for multicomponent reaction promoted by $NbCl_5$.

Finally, we can conclude that the use of niobium pentachloride as a catalyst in the multicomponent reaction between methyl acetoacetate (**1**) and benzaldehyde derivatives (**2 a-g**) produces new 4*H*-pyran derivatives with good yields, under mild reaction conditions (room temperature) in a very efficient manner.

Acknowledgments

The authors would like to thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Proc. 2016/01599-1), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (Proc. 302753/2015-0) and Pró-Reitoria de Pesquisa (PROPe-UNESP) for their financial support. We would also like to thank CBMM – Companhia Brasileira de Mineralogia e Mineração for the $NbCl_5$ samples.

Supplementary data

Supplementary data associated with this article can be found in the online version.

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9. **General procedure for synthesis of 4*H*-pyran derivatives:**
In a solution of niobium pentachloride (1.0 mmol) and anhydrous dichloromethane (2.0 ml), we added methyl acetoacetate (2.0 mmols) and the respective benzaldehyde derivative (1.0 mmol). Each reagent dissolved in 1.0 ml of dichloromethane. The reaction was maintained at room temperature under constant agitation. In order to stop the reaction, distilled water (5.0 mL) was added. The mixture was extracted with dichloromethane (20.0 mL). The organic portion was washed with saturated sodium bicarbonate (2 x 20.0 mL), saturated sodium chloride (2 x 20.0 mL) and anhydrous magnesium sulfate. The solvent was removed on rota-evaporator and the products were purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate (7:3).
Dimethyl 2,6-dimethyl-4-phenyl-4*H*-pyran-3,5-dicarboxylate (**3a**) NMR ^{1}H (400 MHz, $CDCl_3$) δ = 2.36 (s, 6H, CH_3), 3.64 (s, 6H, CH_3), 4.76 (s, 1H, -CH), 7.22 (m, 5H, Ar-H); NMR ^{13}C (100 MHz, $CDCl_3$), δ =18.7, 38.3, 51.3, 108.2, 126.6, 128.1, 145.3, 158.5, 167.1.

***Highlights**

- 4*H*-pyran derivatives are an important class of natural organic compounds with several biological and pharmacological activities.

- Synthesis of new 4*H*-pyran derivatives by Multicomponent Reaction (MCR) promoted by niobium pentachloride

- $NbCl_5$ promotes the synthesis of 4*H*-Pyran derivatives in mild conditions, with low production cost and with good yields.