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## Lewis acid-catalyzed one-pot sequential reaction for the synthesis of $\alpha$ -halogenated $\beta$ -keto esters

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## ABSTRACT

A Lewis acid-catalyzed one-pot sequential transformation of  $\beta$ -keto esters, aromatic aldehydes, and NCS/ NBS was reported. The reaction proceeds by way of Knoevenagel condensation/Nazarov cyclization/halogenation to give  $\alpha$ -chloro- and  $\alpha$ -bromo- $\beta$ -keto esters in moderate yields with high diastereoselectivities. However, several aromatic aldehydes with electron-withdrawing substituents afforded unexpected  $\alpha$ , $\beta'$ dichloro- $\beta$ -keto esters in good to high yields.

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 $\alpha$ -Chlorinated and  $\alpha$ -brominated carbonyl compounds are versatile intermediates in organic synthesis, natural product chemistry, and in biomedical and pharmaceutical sciences.<sup>1-4</sup> Therefore, the preparation of the structural complex and diverse chlorinated and brominated compounds has received much attention in synthetic chemistry.<sup>5–18</sup> The most commonly used process is the 'stop and go' sequence of individual reactions. However, the quest for efficient methods for the construction of the halogenated molecules is just at the beginning. Multicomponent sequential transformations try to meet these more challenging requirements because this new strategy favors the formation of several bonds in one-pot by using a single catalyst, without the need for isolation and purification of the intermediates.<sup>19,20</sup> For example, Lectka and coworkers have developed a one-pot halogenation/esterification process of acyl halides using perhaloquinone-derived reagents as the halogen source. The reactions were catalyzed by benzoylquinine.<sup>21</sup> Togni and co-workers presented [TiCl<sub>2</sub>(TADDOLato)]-catalyzed one-pot heterodihalogenation of  $\beta$ -keto esters with F-TEDA and NCS to afford  $\alpha$ -chloro- $\alpha$ -fluoro- $\beta$ -keto esters in moderate to good yields.<sup>22</sup> Apparently one-pot multistep reactions involving C-X bond-formation remain very rare, and the design of novel catalytic systems is still in great demand for the rapid advancement of the fields of organic synthesis and medicinal agents. As a part of a research program aimed at the development of catalytic methods for the construction of halogenated molecules, we recently reported several one-pot multistep sequential transformations for the synthesis of organofluorine compounds.<sup>23-25</sup> Herein, we wish to present a Lewis acid-catalyzed one-pot sequential reaction of  $\beta$ -keto esters, aromatic aldehydes, and NCS/NBS to give  $\alpha$ -chloro and  $\alpha$ -bromo- $\beta$ -keto esters.

This one-pot sequence is a three-component reaction comprising an aromatic  $\beta$ -keto ester, an aromatic aldehyde, a halogenating agent (NXS: X = Cl, Br, I), and a simple Lewis acid, which is capable of catalyzing each step of this triple transformation of Knoevenagel condensation/Nazarov cyclization/halogenation (Scheme 1). In the presence of AlCl<sub>3</sub>, the reaction of methyl benzoylacetate and benzaldehyde with NCS in nitroethane affords the desired product 1a in moderate yield (50%) with high diastereoselectivity (trans/cis: 26/ 1) (Table 1, entry 1). When the reaction solvent was changed to toluene, CHCl<sub>3</sub>, DMF, or CH<sub>3</sub>CN, no desired product was obtained, thus EtNO<sub>2</sub> gave the best results. Next we tested the possibility of using NBS and NIS in this one-pot sequential reaction. Interestingly, the desired brominated product **1h** was obtained in good yield (62%) with excellent diastereoselectivity (trans/cis: 29/1) (Table 1, entry 8), whereas the iodinated product was not observed. Various other β-keto esters and aromatic aldehydes were converted to their corresponding  $\alpha$ -chlorinated and  $\alpha$ -brominated products (**1b**-g and 1i-k) in moderate to good yields with excellent diastereoselectivties using this procedure (Table 1, entries 2–7 and 9–11).<sup>26</sup> Surprisingly, the dichlorinated reaction occurred on the aromatic ring and  $\alpha$ -position of ethyl 3-(3'-methoxyphenyl)-3-oxopropanoate in the presence of over 2 equiv of NCS. However, this phenomenon was not observed for other substrates and NBS.

It is noteworthy that the one-pot sequential reaction of methyl benzoylacetate and 3,4-dichlorobenzaldehyde with NCS in nitroe-thane gave  $\alpha$ , $\beta'$ -dichloro- $\beta$ -keto ester **2a** in high yield.<sup>27</sup> The major diastereomer for the product **2a** was recrystallized in pure form by





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Scheme 1.





using an ethyl acetate-petroleum mixture. The relative stereochemistry confirmed by X-ray crystallography shows the anti configuration (Scheme 2).<sup>28</sup> In the presence of AlCl<sub>3</sub>, the reaction of methyl benzoylacetate and 3,4-dichlorobenzaldehyde without NCS afforded the Knoevenagel condensation product in nearly quantitative yield. However, the Nazarov product was not observed in this reaction system. These results indicated that the electron-withdrawing substituents on the alkylidene moiety of β-keto esters could restrain  $4\pi$ -electrocyclization of the polarized enone. The mechanism for this intriguing sequential reaction is not clear at this stage.<sup>29</sup> When NCS was replaced by NBS or NIS, only the Knoevenagel condensation intermediate was obtained, and the corresponding halogenated products were not observed. Several  $\alpha,\beta'$ -dichloro- $\beta$ -keto esters 2b-i were also obtained from the one-pot sequential reaction of aromatic β-keto esters with 3,4-dichlorobenzaldehyde, 4-chlorobenzaldehyde, and 4-trifluoromethyl benzaldehyde in the presence of NCS and AlCl<sub>3</sub> (Fig. 1).<sup>30</sup> Interestingly, the position differences of the electron-donating substituents on the phenyl ring of  $\alpha$ -keto esters also changed the reaction course dramatically. For example, methyl 3-(4'-methoxyphenyl)-3-oxopropanoate gave  $\alpha,\beta'$ -diDownload English Version:

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