



## 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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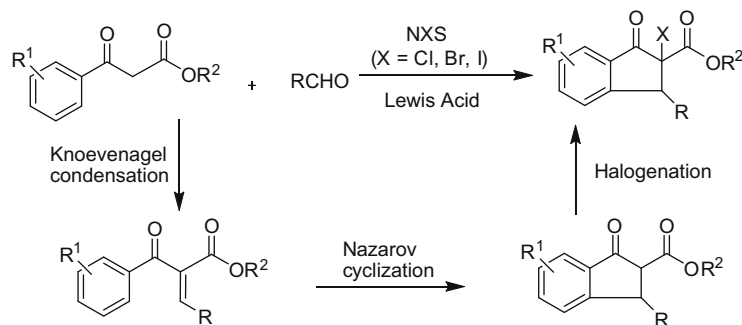
$\alpha$ -Chlorinated and  $\alpha$ -brominated carbonyl compounds are versatile intermediates in organic synthesis, natural product chemistry, and in biomedical and pharmaceutical sciences.<sup>1–4</sup> Therefore, the preparation of the structural complex and diverse chlorinated and brominated compounds 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 co-workers 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 pres-

ent 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.

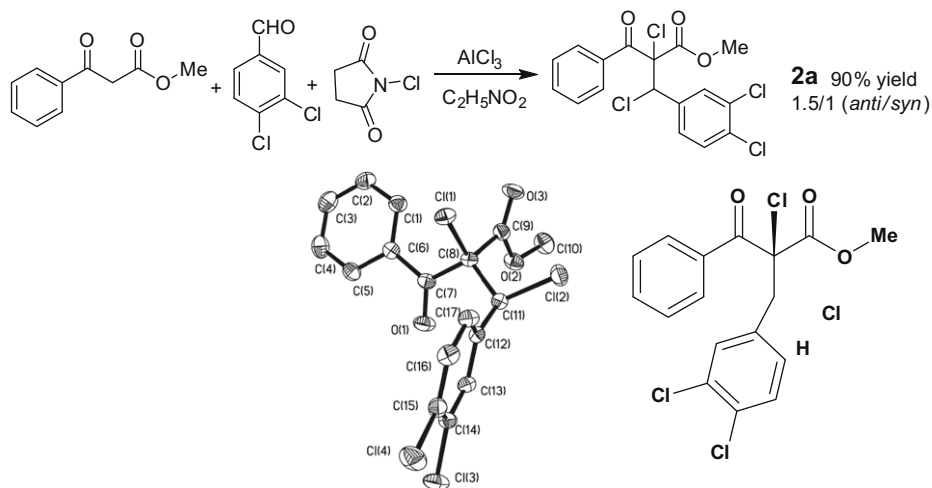
This one-pot sequence is a three-component reaction comprising an aromatic  $\beta$ -keto ester, an aromatic aldehyde, a halogenating agent (NXS: X = Cl, Br, I), and a simple Lewis acid, which is capable of catalyzing each step of this triple transformation of Knoevenagel condensation/Nazarov cyclization/halogenation (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  $\beta$ -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 diastereoselectivities 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 nitroethane 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.



Scheme 2.

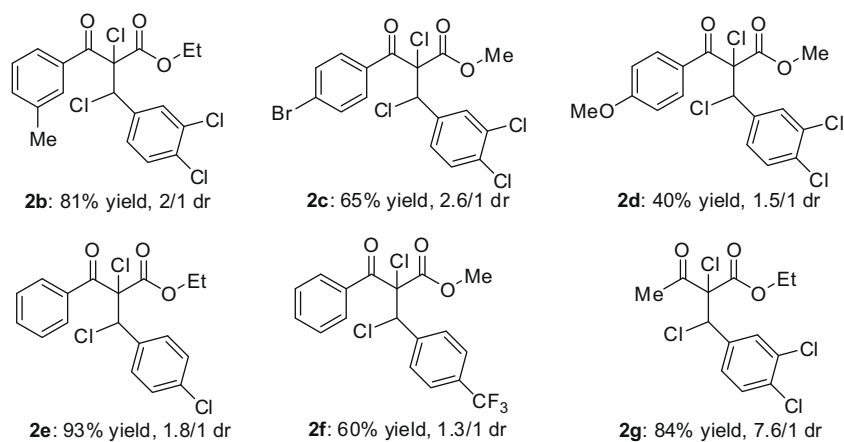


Figure 1.

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  $\text{AlCl}_3$ , 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  $\beta$ -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  $\beta$ -keto esters with 3,4-dichlorobenzaldehyde, 4-chlorobenzaldehyde, and 4-trifluoromethyl benzaldehyde in the presence of NCS and  $\text{AlCl}_3$  (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  $\alpha,\beta'$ -di-

**Table 1**  
Lewis acid-catalyzed one-pot sequential reaction of  $\beta$ -keto ester, aldehyde, and NCS/NBS

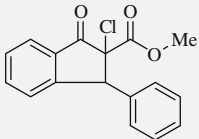
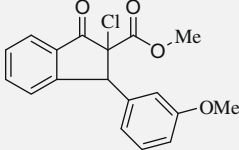
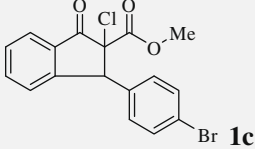
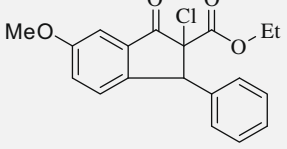
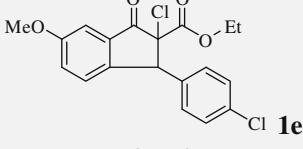
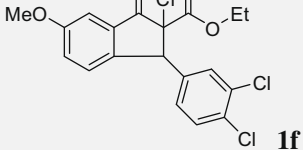
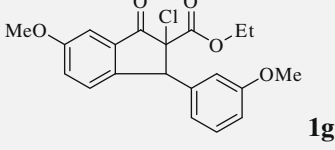
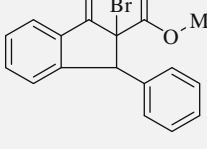
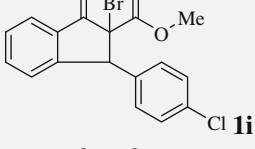
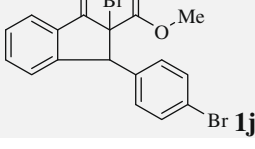
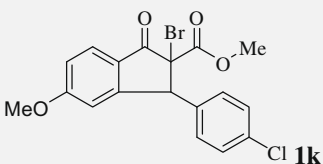
Entry	Halogenating reagent	Product <sup>a</sup>	Yield <sup>b</sup> (%)	Trans/cis <sup>c</sup>
1	NCS	 <b>1a</b>	50	26/1
2	NCS	 <b>1b</b>	45	22/1
3	NCS	 <b>1c</b>	53	28/1
4	NCS	 <b>1d</b>	32	25/1
5	NCS	 <b>1e</b>	63	25/1
6	NCS	 <b>1f</b>	32	25/1
7	NCS	 <b>1g</b>	37	28/1
8	NBS	 <b>1h</b>	62	29/1
9	NBS	 <b>1i</b>	42	22/1
10	NBS	 <b>1j</b>	22	24/1

Table 1 (continued)

Entry	Halogenating reagent	Product <sup>a</sup>	Yield <sup>b</sup> (%)	Trans/cis <sup>c</sup>
11	NBS		31	24/1

<sup>a</sup>  $\beta$ -Keto ester (1.0 equiv), aldehyde (1.2 equiv),  $\text{AlCl}_3$  (2.0 equiv) in  $\text{EtNO}_2$  at room temperature for 24–48 h, then NCS/NBS (1.2 equiv) was added and stirred for 12 h at 80 °C. All products were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, and mass spectroscopy.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by  $^1\text{H}$  NMR.

chloro- $\beta$ -keto ester **2d**, whereas methyl 3-(3'-methoxyphenyl)-3-oxopropanoate proceeded by way of a Lewis acid-catalyzed Knoevenagel condensation/Nazarov cyclization/chlorination sequence to afford chlorinated 1-indanone derivative **1f** in moderate yield with high diastereoselectivity (Table 1, entry 6). In addition, ethyl 3-oxobutanoate also gave the corresponding  $\alpha$ ,  $\beta'$ -dichloro- $\beta$ -keto ester **2g** in 84% yields and with 7.6/1 diastereoselective ratio.

In conclusion, we have demonstrated a Lewis acid-catalyzed one-pot sequential reaction via triple transformation of Knoevenagel condensation/Nazarov cyclization/halogenation to afford chlorinated and brominated 1-indanone derivatives in moderate yields with high diastereoselectivities. In this catalytic system, unexpected  $\alpha$ ,  $\beta'$ -dichloro- $\beta$ -keto esters were obtained by the use of several aromatic aldehydes bearing electron-withdrawing substituents. Further investigation of the reaction mechanism, as well as the development of catalytic asymmetric systems are currently being explored and will be reported in due course.

## Acknowledgments

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## References and notes

- De Kimpe, N.; Verhé, R. *The Chemistry of  $\alpha$ -Haloketones,  $\alpha$ -Haloaldehydes, and  $\alpha$ -Haloamines*; John Wiley & Sons: New York, 1990.
- Larock, R. C. *Comprehensive Organic Transformations*, second ed.; VCH: New York, 1999.
- Thomas, G. *Medicinal Chemistry: An Introduction*; John Wiley & Sons: New York, 2000.
- Feske, B. D.; Kaluzna, I. A.; Stewart, J. D. *J. Org. Chem.* **2005**, *70*, 9654.
- Mei, Y.; Bentley, P. A.; Du, J. *Tetrahedron Lett.* **2008**, *49*, 3802.
- Meshram, H. M.; Reddy, P. N.; Vishnu, P.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 991.
- Halland, N.; Lie, M. A.; Kjærsgaard, A.; Marigo, M.; Schiøt, B.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 7083.
- Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219.
- Meshram, H. M.; Reddy, P. N.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 623.
- Meketa, M. L.; Mahajan, Y. R.; Weinreb, S. M. *Tetrahedron Lett.* **2005**, *46*, 4749.
- Halland, N.; Branton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
- Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
- Marigo, M.; Bachmann, S.; Halland, N.; Branton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507.
- Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, *10*, 2133.
- Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038.
- Wang, C.; Tunge, J. *Chem. Commun.* **2004**, 2694.
- Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429.
- Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425.
- Review, see: Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.
- Review, see: Guillena, G.; RamUn, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693.
- Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531.
- Frantz, R.; Hintermann, L.; Perseghini, M.; Broggin, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709.
- Zhang, G.-W.; Wang, L.; Nie, J.; Ma, J.-A. *Adv. Synth. Catal.* **2008**, *350*, 1457.
- Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, 2284.
- Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053.
- General procedure for Knoevenagel condensation/Nazarov cyclization/electrophilic chlorination: anhydrous  $\text{AlCl}_3$  (0.2 mmol) was added to a solution of  $\beta$ -keto ester (0.1 mmol) and aldehydes (0.12 mmol) in  $\text{EtNO}_2$  (1.0 mL) under an inert atmosphere and the resulting mixture was stirred at room temperature for 24–48 h (monitored by TLC). Then a solution of NCS/NBS (0.12 mmol) in 1.0 mL  $\text{EtNO}_2$  was added and the reaction mixture was heated to 80 °C for 12–24 h (monitored by TLC). After cooling to ambient temperature, the reaction was quenched by 2 M HCl, and the reaction mixture was extracted with ethyl acetate, washed with brine, dried by  $\text{MgSO}_4$ , filtered, and concentrated under vacuum. The crude oil was purified by silica gel flash chromatography to give the desired product.
- The reaction of methyl benzoylacetate and 3,4-dichlorobenzaldehyde with NFSI in nitroethane proceeded by way of a Lewis acid-catalyzed Knoevenagel condensation/Nazarov cyclization/fluorination sequence to afford fluorinated 1-indanone derivative in 62% yield with high diastereoselectivity (trans/cis: 25/1). The electrophilic fluorination trapping as a terminating step for Nazarov cyclization may facilitate catalyst turnover.
- CCDC 758804 contains the supplementary crystallographic data for the product anti-2a. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- Electrophilic chloronium ion could be generated from  $\alpha$ -alkylidene  $\beta$ -keto ester and opened by nucleophilic chloride. Relative reported, see: Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273.
- General procedure for Knoevenagel condensation/chlorination: anhydrous  $\text{AlCl}_3$  (0.2 mmol) was added to a solution of  $\beta$ -keto ester (0.1 mmol) and aldehydes (0.1 mmol) in  $\text{EtNO}_2$  (1.0 mL) under an inert atmosphere and the resulting mixture was stirred at room temperature for 24–48 h (monitored by TLC). Then a solution of NCS (0.20 mmol) in 1.0 mL  $\text{EtNO}_2$  was added and the reaction mixture was heated to 110 °C for 12 h. After cooling to ambient temperature, the reaction was quenched by 2 M HCl, and the reaction mixture was extracted with ethyl acetate, washed with brine, dried by  $\text{MgSO}_4$ , filtered, and concentrated under vacuum. The crude oil was purified by silica gel flash chromatography to give the desired product.