Dual Roles of Ynoates: Desymmetrization of Dicarboxylic Acids using Trialkylamines as Alkyl Equivalents

Xianjun Xu,^a Liliang Huang,^a Xiaoying Yin,^{*a} Erik V. Van der Eycken^{b,c} and Huangdi Feng^{*a}

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A novel method has been developed for the desymmetrization of aromatic dicarboxylic acids by employing an esterification reaction/conjugate addition of a carboxyl group to ynoates, which can trigger a coupling reaction. This one-pot cascade transformation, utilizing trialkylamines as alkyl sources for esterification, and ethyl propiolate as a protective or coupling reagent for carboxyl functions (hydrolysis, amidation, esterification, thioesterification), leads to asymmetric dicarbonyl target skeleton in a selective manner.

accepted 11/09

Introduction

The condensation reaction of carboxylic acids is the most fundamental, and important process in organic chemistry.¹ Among various conceivable scenarios, a double carboxyl functionalization of dicarboxylic acids is of particular interest, holding promise for the preparation of dicarbonyl compounds that possess significant medicinal value.² Examples are the antimalarial (+)-SJ733,³ the anti-platelet aggregating drug picotamide,⁴ and the anti-inflammatory and antipyretic benorilate⁵ (Figure 1a). In addition, these analogues also can be found in material sciences,⁶ especially for polyethylene terephthalate (Figure 1b). In view of the fact that the difunctionalization of dicarboxylic acids is often nonselective, it is important to develop desymmetric activation approaches. The vast majority of reported asymmetric aromatic dicarboxylic

Figure 1. a), b) Representative Dicarbonyl Skeletons. c) Traditional Protocol for Dicarboxylic Derivates.

Scheme 1. Development of Acetylene-Driven Reaction

derivates are achieved by successive diesterification, mono-hydrolysis, and condensation between the in situ generated acyl halide intermediate and a suitable nucleophile (Figure 1c).⁷ However, complex operations, low atom economy, and harsh reaction conditions are hampering this protocol. Hence, rapid and flexible methods, that can produce asymmetric dicarbonylskeletons from simple starting materials, remain highly desirable.

Recently, our laboratory has been engaged in the development of synthetic methods using α -acyl enol ester intermediates (Scheme 1, eq 1).⁸ In this reaction, we observed the formation of methyl 3-(diethylamino)acrylate as a byproduct generated from methyl propiolate and triethylamine that has been shown to be a very useful nitrogen source via C–N bond activation for constructing the corresponding N-containing compounds.⁹ Although tertiary amines are now recognized as fundamental synthetic building blocks, they remain challenging to explore as carbon sources for C–N bond cleavage.¹⁰ In particular, the aza-Claisen rearrangement of N-alkenyl ammonium salt intermediates represents one of the most reliable approaches on this research theme (Scheme 1, eq 2).¹¹ To the best of our knowledge, the intermolecular esterification of carboxylic acids through trapping of carbonium

^a College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, 333 Longteng Road, Shanghai, 201620, China. E-mail: hdfeng@sues.edu.cn; ncyxoy@163.com

^b Laboratory for Organic and Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, KU Leuven, Celestijnenlaan 200F, Leuven 3001, Belgium.

^c Peoples' Friendship University of Russia (RUDN University), 6 Miklukho-Maklaya Street, Moscow 117198, Russia.

†Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

ions generated from tertiary amines, has not been described to date. Framed by this chemistry (Scheme 1, eq 2) and the existing transformations of enol ester intermediates,¹² we sought to apply ynoates as protectant and activating reagents, as well as trialkylamines as alkyl equivalents for the alternative functionalization of aromatic dicarboxylic acids to afford desymmetrical diesters, which could directly undergo coupling with several nucleophiles to provide unsymmetrical dicarboxylic acid derivatives (Scheme 1, eq 3).

Results and discussion

Our study commenced with the reaction of isophthalic acid **1a**, and triethylamine **2a** for the optimization of protecting reagent and reaction conditions (Table 1). To our delight, when methyl propiolate **3a** was introduced in THF at 65 °C for 8 h, the target unsymmetrical product **4** was achieved in 25% yield with dienol ester byproduct **4'** (entry 1). Note that no additional metal catalyst or additive was required for this desymmetrization reaction. Encouraged by this result, a range

little better yield than methyl propiolate. Screening of the solvents (entries 5–12) revealed that chloroform delivered the best results (entry 7). However, switching to the polar solvents (1,4-dioxane, acetonitrile and DMF) appeared to be deleterious for the reaction (entries 10–12). This result might be owing to the higher water content of polar solvents. Therefore, anhydrous chloroform was examined, this resulted in an improved yield of 61% of the target compound **4** (entry 13). Next, we targeted the amount of triethylamine **2a** and ethyl propiolate **3b** (entries 14–18). As a result, the reaction yield could be improved to 68% (entry 15). The reaction temperature played an important role in affecting the reaction. When the temperature was raised to 75 °C, the desired process was significantly improved as the yield increased to 77% (entry 19). Lowering the temperature to 50 °C resulted in a diminished yield (entry 20).

Table 2. Chemoselectivity Study in the Desymmetrical Esterification^a

Table 1. Protecting Agent and Condition Screening^a

entry	agent 3 [equiv]	solvent	temp. [°C]	yield [%] ^b
1	3a , R = MeO, 2.2	THF	65	25
2	3b , R = EtO, 2.2	THF	65	29
3	3c , R = <i>t</i> BuO, 2.2	THF	65	28
4	3d , R = Me, 2.2	THF	65	4
5	3b , R = EtO, 2.2	DCM	40	21
6	3b , R = EtO, 2.2	toluene	65	12
7	3b , R = EtO, 2.2	chloroform	65	55
8	3b , R = EtO, 2.2	DCE	65	38
9	3b , R = EtO, 2.2	chlorobenzene	65	30
10	3b , R = EtO, 2.2	dioxane	65	trace
11	3b , R = EtO, 2.2	acetonitrile	65	n.d.
12	3b , R = EtO, 2.2	DMF	65	n.d.
13	3b , R = EtO, 2.2	chloroform ^c	65	61
14 ^d	3b , R = EtO, 2.2	chloroform ^c	65	63
15 ^e	3b , R = EtO, 2.2	chloroform ^c	65	68
16 ^f	3b , R = EtO, 2.2	chloroform ^c	65	62
17	3b , R = EtO, 1.8	chloroform ^c	65	47
18	3b , R = EtO, 2.6	chloroform ^c	65	66
19 ^e	3b , R = EtO, 2.2	chloroform ^c	75	77
20 ^e	3b , R = EtO, 2.2	chloroform ^c	50	65

^aGeneral conditions: a stirred solution of isophthalic acid (0.5 mmol), agent **3** (1.1 mmol) in solvent (2 mL) was added triethylamine (0.55 mmol) in solvent (1 mL) over 10 min, and the mixture was stirred for 8 h at the intended temperature. ^bYield of isolated products **4**, n.d. = not determined. ^cDry chloroform. ^dTriethylamine (0.4 mmol). ^eTriethylamine (0.8 mmol). ^fTriethylamine (1.0 mmol).

of different coupling reagents **3b**–**3d** were evaluated (entries 2–4). It was found that ethyl and *t*-butyl propiolate furnished a

^aReactions conditions: a mixture of aromatic dicarboxylic acid (0.5 mmol), ethyl propiolate (1.1 mmol) in dry chloroform (2 mL) was slowly added trialkylamine (0.8 mmol in dry chloroform (1 mL)) over 10 min, and the mixture was stirred for 5–8 h at 75 °C; yield of isolated products.

The reaction scope was evaluated using activation reagent **3b**, various dicarboxylic acids and tertiary amines (Table 2). A diverse set of isophthalic acids bearing both electron-donating

and -withdrawing groups reacted well, providing the target products **4a–4c** in high yields. Remarkably, an amino-containing substrate was also tolerated, and the corresponding desymmetric product **4d** was obtained in 33% yield. Next, terephthalic acids underwent the transformation smoothly, furnishing the desired products **4e**, and **4f** in good yields. Naphthyl, biphenyl, and thienyl derivatives were then explored, leading to the corresponding products **4g–4j** in the yields of 53–75%. However, no conversion was observed when pyridine-2,6-dicarboxylic acid, and fumaric acid were investigated as the substrate (**4k**, **4l**), where pyridine-2,6-dicarboxylic acid afforded diethyl pyridine-2,6-dicarboxylate as byproduct. Further studies indicated that the approach can be extended to a range of tertiary amines with various alkyl groups such as propyl, butyl, amyl, hexyl, and octyl, providing the corresponding products **4m–4q** in moderate yields. However, tribenzylamine appeared to be unsuitable for this reaction (**4r**).

Scheme 2. Proposed Pathway for the Synthesis of **4a**

A possible pathway for the synthesis of **4a** is described in Scheme 2. Reaction of ethyl propiolate with trialkylamine will first generate the zwitterionic intermediate **A**.^{11a,b} Subsequent Michael addition of isophthalic acid to intermediate **A**, followed by NEt_3 elimination produced the enol ester **B**.¹³ This species could undergo a similar Michael addition/ NEt_3 elimination to give dienol ester byproduct **4a'** (Path A). Alternatively, a nucleophilic ethyl substitution accessed between the intermediates **A** and **B**, providing the desired product **4a** with ethyl 3-(diethylamino)-acrylate as a byproduct (Path B).¹⁴

To elucidate the utility of the new methodology developed in this effort, we investigated the *in situ* condensation of the enol ester group with simple N, O and S nucleophiles (Table 3). First, the C–N coupling reaction was tested under our standard reaction conditions. To our delight, various primary amines were suitable for this coupling transformation, giving the amide products **5Na–5Ne** in good yields. However, aniline was not compatible with our reaction conditions (**5Nf**). All of the tested dicarboxylic acids including phenyl, and naphthyl diacids reacted smoothly to provide the corresponding products **5Ng–5Ni** in high yields. Further investigation on the substrate scope revealed that the strategy could be extended to C–O coupling

Table 3. Scope of Desymmetric Difunctionalization of Dicarboxylic Acids^a

^aReaction conditions: a mixture of aromatic dicarboxylic acid (0.5 mmol), ethyl propiolate (1.1 mmol) in dry chloroform (2 mL) was slowly added trialkylamine (0.8 mmol) in dry chloroform (1 mL) over 10 min, and the mixture was stirred for 5–8 h at 75 °C; then Nu-H (Nu = NRR', OR, SR) (1.5 mmol) was added, and stirred for 3–10 h; yield of isolated products.

systems. In each case, selective desymmetrization occurred cleanly, and ester products **5Oa–5Om** were isolated in moderate to good yields. Although methanol did not react with isophthalic acid under the optimized conditions (**5Og**), a less nucleophilic alcohol, or sterically hindered substrate was well tolerated, delivering the products **5Oh** in 55%, and **5Oi** in 35% yields, respectively. Interestingly, a drug prednisolone was also effective in the esterification of isophthalic acid (**5Oj**). A range of trialkylamines for this transformation was examined, delivering

the products **50k–50m** in good yields. Similar efficiencies were observed for C–S bond forming desymmetrization of isophthalic acid, affording access to thioester products **55a–55f**. In the case of thiophenols (**55a**, **55b**), substituents had an important influence on the C–S coupling, as 2-methylbenzenethiol resulted in no product formation. Different alkyl-substituted thiols proved to be viable substrates for this reaction, giving the corresponding products (**55c–55f**) in satisfactory yields.

Further application of this desymmetric reaction was also explored. Monoesterification products **6a–6e** were successfully synthesized by the in situ hydrolysis of the enol ester species (Scheme 3a).¹⁵ In this reaction, ethyl propiolate was served as a protective agent for the carboxyl group. Thus, a novel strategy for protection and deprotection of one carboxyl group of dicarboxylic acids to give the corresponding monoesters was realized. Moreover, to demonstrate the synthetic versatility of these desymmetrizations, several transformations of products **5** were performed (Scheme 3b). Initially, the A³ reaction of **50e** with *N*-methylbenzylamine, and butyraldehyde was examined,¹⁶ and the target product **7a** was gained in excellent yield. Next, treatment of electron-rich **5Na** derivative with the condensation reagent POCl₃ facilitated Bischler-Napieralski reaction to afford a 3,4-dihydroisoquinoline **7b**.¹⁷ To our delight, when the aniline was employed in the amidation of compound **50h**,¹⁸ the corresponding product **5Nf** was obtained. It is worth noting that this transformation overcame the limitation of the type of amine in the above method, where the aniline was not suitable for the formation of the corresponding amide through the enol ester (see Table 3, **5Nf**).

Scheme 3. Further Application and Transformations

Conclusions

In summary, we have developed a new divergent protocol for the efficient desymmetrization of aromatic dicarboxylic acids. This transformation relies on the use of enoates to protect the carboxyl group, and activate the trialkylamine C–N bond, enabling direct access to enol ester-containing diester derivatives **4**. Notably, introduction of the enol ester group is

efficiently carried out in situ coupling reaction of the generated species **4** with various nucleophiles to produce asymmetric dicarbonylskeletons. Facile operation in open-air, metal-free, and one-pot process make this method practical and attractive.

Conflict of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the generous financial support by the Natural Science Foundation of Shanghai (15ZR1418800), the China Postdoctoral Science Foundation (2016M601681), the Opening Project of Shanghai Key Laboratory of Chemical Biology, and the Shanghai University of Engineering Science (nhrc-2015-15). We also acknowledge the support of RUDN University Program 5-100.

Notes and references

- Representative reviews: (a) A. Ojeda-Porras, D. Gamba-Sánchez, *J. Org. Chem.*, 2016, **81**, 11548; (b) R. M. de Figueiredo, J. S. Suppo, J. M. Campagne, *Chem. Rev.*, 2016, **116**, 12029; (c) H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 2714; (d) S. Fletcher, *Org. Chem. Front.*, 2015, **2**, 739; (e) M. Tsakos, E. S. Schaffert, L. L. Clement, N. L. Villadsena, T. B. Poulsen, *Nat. Prod. Rep.*, 2015, **32**, 605; (f) E. Dimitrijević, M. S. Taylor, *ACS Catal.*, 2013, **3**, 945; (g) M. H. Liu, G. H. Ouyang, D. Niu, Y. T. Song, *Org. Chem. Front.*, 2018, DOI:10.1039/C8QO00620B.
- Selected examples: (a) X. J. Liu, X. X. Shi, Y. L. Zhong, N. Liu, K. Liu, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6591; (b) S. Thum, A. K. Kokornaczky, T. Seki, M. de Maria, N. V. O. Zacarias, H. de Vries, C. Weiss, M. Koch, D. Schepmann, M. Kitamura, N. Tschammer, L. H. Heitman, A. Junker, B. Wünsch, *Eur. J. Med. Chem.*, 2017, **135**, 401. (c) E. Serrao, Z. L. Xu, B. Debnath, F. Christ, Z. Debyser, Y. Q. Long, N. Neamati, *Bioorg. Med. Chem.*, 2013, **21**, 5963.
- (a) D. M. Floyd, P. Stein, Z. Wang, J. Liu, S. Castro, J. A. Clark, M. Connelly, F. Zhu, G. Holbrook, A. Matheny, M. S. Sigal, J. Min, R. Dhinakaran, S. Krishnan, S. Bashyum, S. Knapp, R. K. Guy, *J. Med. Chem.*, 2016, **59**, 7950.
- M. Milani, A. Longoni, M. Maderna, *Br. J. Clin. Pharmacol.*, 1996, **42**, 782.
- E. Oskay, F. Aksu, M. I. Cingi, K. Erol, M. Fidan, *J. Pharm. Sci.*, 1989, **78**, 460.
- (a) P. T. McGrail, *Polym. Int.*, 1996, **41**, 103; (b) S. Bourbigot, X. Flambar, *Fire Mater.*, 2002, **26**, 155; (c) K. Yo. Yoon, G. B. Dong, *Angew. Chem. Int. Ed.*, 2018, **57**, 8592.
- Selected examples: (a) D. Kalsi, N. Barsu, B. Sundararaju, *Chem. Eur. J.*, 2018, **24**, 2360; (b) Z. W. Yang, Q. Zhang, Y. Y. Jiang, L. Li, B. Xiao, Y. Fu, *Chem. Commun.*, 2016, **52**, 6709; (c) X. H. Guan, P. H. Luo, Q. J. He, Y. Z. Hu, H. Z. Ying, *Molecules*, 2017, **22**, 32.
- X. J. Xu, H. D. Feng, L. L. Huang, X. H. Liu, *J. Org. Chem.*, 2018, **83**, 7962.

- 9 (a) Q. Wang, Y. Su, L. Li, H. Huang, *Chem. Soc. Rev.*, 2016, 45, 1257; (b) Q. M. Zhu, Q. H. Yuan, M. W. Chen, M. Q. Guo, H. M. Huang, *Angew. Chem. Int. Ed.*, 2017, 56, 5105; (c) S. Bao, B. Zhaorigetu, B. Agula, M. Baiyin, M. Jia, *J. Org. Chem.*, 2014, 79, 803; (d) S. G. Dawande, B. S. Lad, S. Prajapati, S. Katukojvala, *Org. Biomol. Chem.*, 2016, 14, 5569; (e) J. Lai, L. Chang, G. Yuan, *Org. Lett.* 2016, 18, 3194; (f) M. Szostak, M. Spain, D. J. Procter, *Angew. Chem. Int. Ed.*, 2013, 52, 7237.
- 10 (a) C. Q. Rao, S. Y. Mai, Q. L. Song, *Org. Lett.*, 2017, 19, 4726; (b) S. G. Wang, S. H. Park, N. Cramer, *Angew. Chem. Int. Ed.*, 2018, 57, 5459; (c) E. E. Blackham, J. P. Knowles, J. Burgess, K. I. Booker-Milburn, *Chem. Sci.*, 2016, 7, 2302; (d) H. Yu, G. Y. Zhang, H. M. Huang, *Angew. Chem. Int. Ed.*, 2015, 54, 10912; (e) M. B. Li, Y. Wang, S. K. Tian, *Angew. Chem. Int. Ed.*, 2012, 51, 2968; (f) X. Q. Hu, Z. Y. Hu, G. D. Zhang, N. Sivendran, L. J. Gooßen, *Org. Lett.* 2018, 20, 4337.
- 11 (a) K. A. Kandeel, J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1*, 1987, 0, 2023; (b) E. Vedejs, M. Gingras, *J. Am. Chem. Soc.*, 1994, 116, 579; (c) C. L. Hugelshofer, V. Palani, R. Sarpong, *Org. Lett.*, 2018, 20, 2649.
- 12 (a) T. Rause, S. Baader, B. Erb, L. J. Gooßen, *Nat. Commun.*, 2016, 7, 11732; (b) L. Hu, S. L. Xu, Z. G. Zhao, Y. Yang, Z. Y. Peng, M. Yang, C. L. Wang, J. F. Zhao, *J. Am. Chem. Soc.*, 2016, 138, 13135; (c) N. Panda, P. Mishra, I. Mattan, *J. Org. Chem.*, 2016, 81, 1047; (d) Y. Z. Wang, Z. X. Wang, Y. X. Li, G. D. Wu, Z. Cao, L. M. Zhang, *Nat. Commun.*, 2014, 5, 3470.
- 13 (a) V. Nair, S. B. V. Sreekumar, N. P. Rath, *Org. Lett.* 2003, 5, 665; (b) M. J. Fan, G. Q. Li, Y. M. Liang, *Tetrahedron* 2006, 62, 6782.
- 14 (a) J. P. Jacob, R. Gopalakrishnan, R. R. Mallia, J. J. Vadakkan, P. A. Unnikrishnan, S. Prathapan, *J. Phys. Org. Chem.*, 2014, 27, 884; (b) J. Yamaguchi, S. Sugiyama, *Tetrahedron, Lett.*, 2016, 57, 4514.
- 15 A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi, K. Ishihara, *J. Am. Chem. Soc.*, 2007, 129, 14775.
- 16 (a) P. F. Zhao, H. D. Feng, H. R. Pan, Z. H. Sun, M. C. Tong, *Org. Chem. Front.*, 2017, 4, 37; (b) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.*, 2012, 41, 3790.
- 17 A. Amelia, C. Alfredo, *J. Org. Chem.*, 2010, 75, 5627.
- 18 (a) G. W. Cline, S. B. Hanna, *J. Am. Chem. Soc.*, 1987, 109, 3087; (b) B. Tan, N. Toda, C. F. Barbas III, *Angew. Chem. Int. Ed.*, 2012, 51, 12538.