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Carboxylic Anhydride Synthesis from γ-Benzyl-L-glutamate and Dimethyl Carbonate

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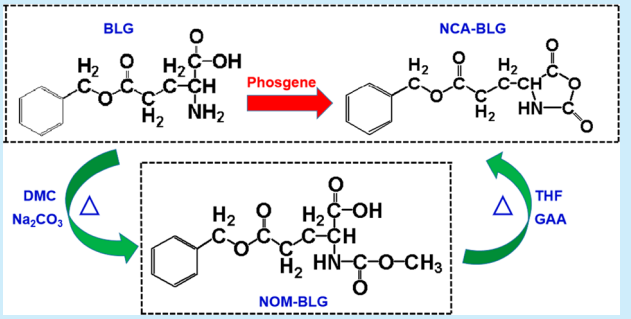
Supporting Information

ABSTRACT: A green, environmentally friendly, and nontoxic method was developed to synthesize carboxylic anhydrides (NCAs) from γ-benzyl-L-glutamate (BLG) and dimethyl carbonate (DMC) though two steps: synthesis of *N*-methoxycarbonyl-γ-benzyl-L-glutamate intermediate (NOM-BLG) and cyclization. The highest yields of NOM-BLG (up to 83.7%) and NCA-BLG (up to 66.7%) were obtained. Most importantly, the use of DMC will open an innovative door to synthesize NCAs.



With the development of protein-directed evolution technology,[1] the diversity of polypeptides and proteins from ring-opening polymerization[2,3] of carboxylic anhydrides (NCAs) has been increasingly investigated for various chemical and biomedical applications,[4−6] such as drug delivery, artificial tissues, etc.[7,8] Therefore, it is extremely indispensable to give more attention to the preparation of NCAs, which are highly useful monomers for preparing polypeptides.[9,10]

The original synthesis methods of NCAs and their applications in the construction of polypeptides were reported by Leuchs[11] in 1906. Subsequently, different synthetic methods using amino acid derivatives and halogenating agents ($SOCl_2$, PBr_3, PCl_3) were developed.[12] Other researchers[13,14] made a breakthrough on direct NCA synthesis through the reaction of amino acids with phosgene, triphosgene, or diphosgene,[15] and the various NCAs and well-defined polypeptides can be obtained from amino acids and phosgene compounds. However, those methods have many disadvantages and limitations because of their lethal toxicity and highly corrosive byproduct, HCl.[16,17] In some other synthetic routes to NCA, methyl chloroformate,[18] NO/O_2,[19] and bis(2,4-dinitrophenyl) carbonate (DNPC)[20] were considered as good cyclization reagents, but they also suffered from the similar toxicity problems.[21] In summary, plenty of restrictions on the NCA synthetic process still exist, incluing being operationally difficult, harmful to the human body, incapable of large-scale production, difficult to obtain high purity products, and so on. Therefore, it is especially necessary to develop an environmentally friendly[22] and nontoxic NCA synthetic route, which will strongly benefit the technological development of polypeptides and protein engineering.

Dimethyl carbonate (DMC) is a suitable and desirable candidate as an alternative to phosgene,[23] and it is completely qualified as an environmental compound to synthesize various chemicals such as polycarbonate,[24] methyl benzoate, furazolidone,[25] etc. DMC can also be considered as an effective carbonylation reagent due to the following advantages compared with bisarylcarbonates, methyl chloroformate, and phosgene.[26,27] (1) The structure of DMC contains some high reactivity functional groups, such as $-CH_3$, CH_3O-, and $-C{=}O$, which are easy to synthesize intermediate products with amino acid derivatives.[28] (2) When the active center site on the carbonyl group is attacked by a nucleophilic substance, $-C{=}O$ will be broken and then recombine to a new substance. After DMC carbonylation, the decomposition byproduct methanol is convenient to handle.[20,29] (3) DMC is nontoxic, much more economical, safely stored, and utilized. Therefore, the employment of DMC will open an innovative door to the synthesis of NCAs.

Herein, we report our preliminary investigation on the synthesis of NCAs of γ-benzyl-L-glutamate **1** from DMC in tetrahydrofuran (THF), and a unique NCA synthetic method that consisted of two steps (Scheme 1) was developed: The first step is the synthesis of intermediate *N*-methoxycarbonyl-γ-benzyl-L-glutamate **3**, and then the pure intermediate was obtained through extraction with hexane or petroleum ether. The influences of various solvents, different temperatures, and DMC/amino acids ratios on the yields of the intermediate were investigated. The second step is the preparation of corresponding NCA from the cyclization of the intermediate. It turned out that THF was a good solvent for the following cyclization reaction due to the poor solubility of NCAs and its extreme sensitivity to water.

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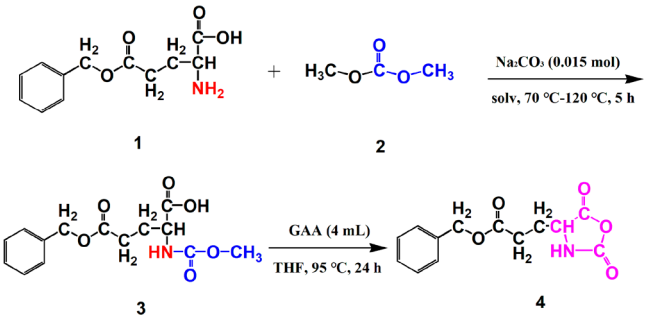
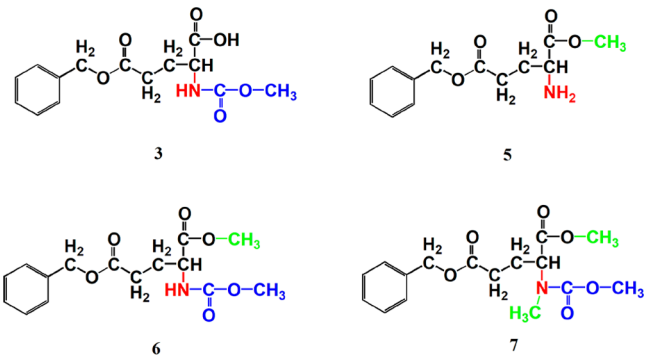
Scheme 1. Reaction Process



1 2 3 4

The characterized results of ^{1}H NMR, ^{13}C NMR, and elemental analysis (Supporting Information) were extremely consistent with the molecular structure of compound **3**, which indicated that the intermediate was successfully synthesized, and it would be applied to carry out the cyclization reaction to synthesize NCA. During the conversion process of DMC, there was the formation of other byproducts from the esterification reaction of the carboxyl group, the methylation of the nitrogen atom, and both (Scheme 2), which resulted in a relatively low yield of the intermediate.

Scheme 2. Products in the Reaction



3 5 6 7

As shown in Figure 1, there was no intermediate formation in three solvents when the temperature was less than 70 °C. The maximum yield reached 83.7, 73.4, and 60.3% in DMF, DMSO, and THF, respectively. However, there was a downward trend of the intermediate yield with an increase in temperature. This tendency was consistent with the reactivity of DMC functional groups (−C═O, $-CH_3$) at different temperatures. Namely, carbonylation took place when a nucleophilic substance mainly attacked the carbonyl carbon of DMC at low temperature, whereas methylation occurred when the nucleophilic reagent primarily attacked the methyl group at high temperature (greater than 90 °C). The highest reactivity of carbonyl carbon appeared at 100 °C, which was conducive for reacting with the nitrogen atom in compound **1**.

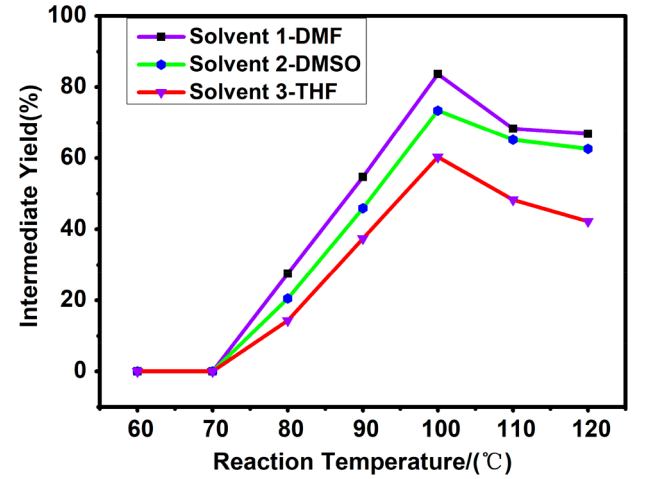


Figure 1. Relationship between the isolated yield (%) and temperature (°C) of compound **3** in three solvents.

The relationship between intermediate yield and BLG/DMC mole ratios is listed in Figure 2. When the BLG/DMC molar ratio was 1:2, the highest yields achieved were 83.7 and 74.6% in DMF and DMSO, respectively. The slightly excess of DMC was indispensable because it would partially volatilize at 100 °C (boiling point 90 °C). Theoretically, there was a competitive reaction between methylation and carbonylation of the nitrogen atom in compound **1**. The electrophilicity of carbonyl groups was much higher than that of methyl group; therefore, the carbonyl groups had advantages to react with the nitrogen atom. On the other hand, excess DMC probably reacted with the carboxyl group in compound **1** to form the corresponding ester, but it was detrimental to the cyclization reaction in the next step. In addition, the unfavorable water byproduct would cause the hydrolysis of DMC and BLG, resulting in significant reduction in the yield of the intermediate. Therefore, it turned out that the optimum BLG/DMC mole ratio was 1:2.

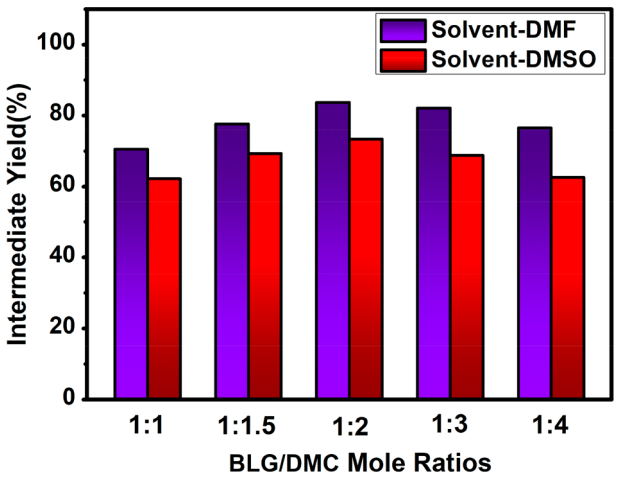


Figure 2. Relationship between the isolated yield (%) and BLG/DMC mole ratios of compound **3** in two solvents.

The influence of various solvents on the intermediate yield was investigated, as indicated in Table 1. The different reaction effects were attributed to the consequence of solvent polarities and solubility of compound **1**. The order of the solvents' polarity strength is as follows: DMSO, DMF, 1,4-dioxane, THF, cyclohexanone, ethyl acetate, dichloromethane and cyclohexane. The strongly polar DMF and DMSO could significantly improve the solubility of compound **1** at the same reaction temperature and time. The formation of a homogeneous solution system promoted the formation of an intermediate. However, compound **1** did not dissolve in these solvents with lower polarity during the reaction, which resulted in no intermediate being obtained in reaction systems. The

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Table 1. Relationship between the Isolated Yield (%) of Compound 3 and Various Solvents

entry	temp (°C)	solvent	time (h)	yield (%)
1	100	DMF	5	83.7
2	100	DMSO	5	73.4
3	100	THF	5	60.3
4	100	1,4-dioxane	5	29.3
5	100	cyclohexanone	5	24.4
6	100	ethyl acetate	5	
7	100	dichloromethane	5	
8	100	cyclohexane	5	

compound **3** formation reaction was significantly dependent on the properties of solvents, and the weak tendency of the self-transfer proton and the strong ability of dissolution would improve the yield of compound **3**.

The same peak positions and molecular fragments of NCA-BLG **4** were detected in the reaction solution, which were perfectly consistent with the standard sample. Therefore, it could be confirmed that compound **4** has been successfully prepared. Other peaks at 5.136 min were attributed to the benzyl alcohol formation from the hydrolysis of compound **3**, which was further confirmed by mass spectrometry (Supporting Information).

To obtain the pure product compound **4**, it was quite essential to strictly control the reaction conditions. Some challenges existed during the synthesis process, such as the immense difficulties preparing a stable cyclic compound, the extreme sensitivity to aqueous environments, and the strong probability of ring-opening polymerization.

As described in Figure 3, the effect of different temperatures on the efficiency of the cyclization reaction has been

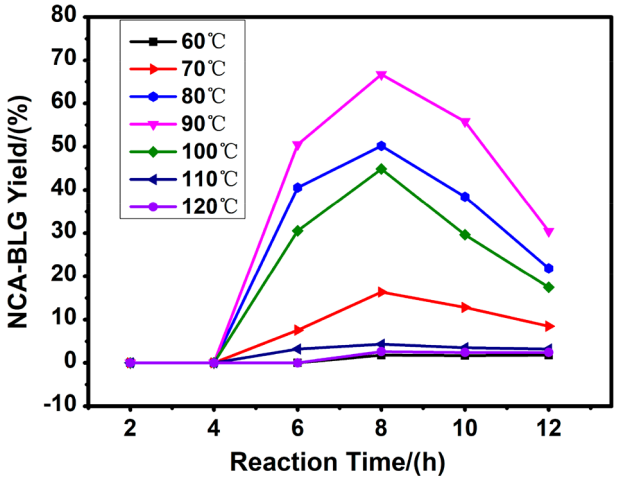

Figure 3. Relationship between the isolated yield (%) and reaction time of compound **4** at different temperatures.

investigated. The results indicated that both low temperature and high temperature were not conducive to the cyclization reaction, and there was almost no compound **4** formation under low-temperature and high-temperature conditions. After 8 h reaction at 90 °C, a maximum yield of 66.7% was detected. There was a downward tendency as the reaction time increased. The cyclization reaction was limited at low temperature, whereas the ring-opening polymerization reaction was prone to occur at high temperature due to the extreme instability of compound **4**. In addition, the benzyl ester underwent hydrolysis, resulting in the formation of benzyl alcohol byproduct.

A novel NCA synthetic technology has been developed by employing DMC instead of phosgene as carbonyl reagent, and this method was environmentally friendly and effortless to operate. The new NCA synthetic method from DMC and amino acid consisted of two steps.

For the carbonylation of DMC with amino acid, the optimized synthesis conditions played a key role in the intermediate product selectivity. When the ratio of BLG and DMC was equal to 1:2, the reaction was carried out at 100 °C for 5 h in aprotic polar solvents, in which the highest yield of 83.7% for compound **3** was obtained in DMF. In the cyclization reaction of compound **3**, glacial acetic acid was employed as cyclization reagent to synthesize compound **4**, and a maximum yield of 66.7% was obtained after cyclization at 90 °C for 8 h.

Although there are still some disadvantages to this process, such as low yield of intermediate and NCA, formation of some byproducts, requirement of an anhydrous environment, etc., this method was indeed highly innovative. Furthermore, the employment of DMC will open an innovative door to the synthesis of NCAs. The power of this synthetic method may be applicable to polypeptide preparation and protein evolution in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03984.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Dietert, R. R.; Dietert, J. M. *Healthcare* **2015**, *3*, 100−129.
(2) Hadjichristidis, N.; Iatrou, H.; Pitsikalis, M.; Sakellariou, G. *Chem. Rev.* **2009**, *109*, 5528.
(3) Wang, C.; Ma, Y.; Su, K.; Li, Z. *Mater. Lett.* **2018**, *231*, 201−204.
(4) Lu, T. C.; Sun, J.; Dong, X.; Chen, X.; Wang, Y.; Jing, X. *Sci. China, Ser. B: Chem.* **2009**, *52*, 2033−2037.
(5) Deming, T. J. *Prog. Polym. Sci.* **2007**, *32*, 858−875.
(6) Kricheldorf, H. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 5752−5784.
(7) Appoh, F. E.; Thomas, D. S. *Macromolecules* **2006**, *39*, 5629−5638.

DOI: 10.1021/acs.orglett.8b03984
Org. Lett. XXXX, XXX, XXX−XXX

(8) Smeenk, J. M.; Schön, P.; Otten, M. B. J.; Speller, S.; Stunnenberg, H. G.; van Hest, J. C. M. *Macromolecules* **2006**, *39*, 2989−2997.
(9) Fan, Y.; Chen, G.; Tanaka, J.; Tateishi, T. *Biomacromolecules* **2005**, *6*, 3051.
(10) Haruma, K.; Kamada, T.; et al. *J. Gastroenterol. Hepatol.* **2000**, *15*, 277−283.
(11) Leuchs, H. J. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 857−861.
(12) Kricheldorf, H. R. *α-Aminoacid-N-Carboxy-Anhydrides and Related Heterocycles*; Springer: Berlin, 1987.
(13) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321.
(14) Takaki, M.; Asami, R.; Hanada, Y.; Ochiai, N. *Polym. Bull.* **1987**, *18*, 105−110.
(15) Daly, W. H.; Poche, D. *Tetrahedron Lett.* **1988**, *29*, 5859−5862.
(16) Habraken, G. J. M.; Wilsens, K. H.; Koning, C. E.; Heise, A. *Polym. Chem.* **2011**, *2*, 1322−1330.
(17) Vayaboury, W.; Giani, O.; Cottet, H.; Deratani, A.; Schue, F. *Macromol. Rapid Commun.* **2004**, *25*, 1221−1224.
(18) Kricheldorf, H. R.; v. Lossow, C.; Schwarz, G. *Macromol. Chem. Phys.* **2005**, *206*, 282−290.
(19) Vayaboury, W.; Giani, O.; Collet, H.; Commeyras, A.; Schue, F. *Amino Acids* **2004**, *27*, 161−167.
(20) Fujita, Y.; Koga, K.; et al. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 5365−5370.
(21) Yamada, S.; Koga, K.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 2527−2532.
(22) Terrasson, V.; Guénin, E. *Novel Magnetic Nanostructures* **2018**, 333−371.
(23) Tundo, P.; Selva, M. J. *Acc. Chem. Res.* **2002**, *35*, 706−716.
(24) Song, M.; Yang, X.; Wang, G. *RSC Adv.* **2018**, *8*, 35014−35022.
(25) Tundo, P.; Musolino, M.; Arico, F. *Green Chem.* **2018**, *20*, 28−85.
(26) Tundo, P.; Anastas, P.; et al. *Pure Appl. Chem.* **2000**, *72*, 1207.
(27) Tundo, P.; Anastas, P.; et al. *Pure Appl. Chem.* **2000**, *72*, 1207−1228.
(28) Anastas, P. T.; Lankey, R. L. *Green Chem.* **2000**, *2*, 289.
(29) Kim, H. K.; Wang, X. S.; et al. *Macromol. Rapid Commun.* **2005**, *26*, 1032−1036.

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Org. Lett. XXXX, XXX, XXX−XXX