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Synthesis of 5-aminolevulinic acid with nontoxic reagents and renewable methyl levulinate†

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Synthesis of 5-aminolevulinic acid (5-ALA) was presented with novel bromination of biobased methyl levulinate (ML), followed by ammoniation and hydrolysis. Copper bromide (CuBr₂) was employed as the bromination reagent with higher selectivity and activity instead of the conventional liquid bromine (Br₂). 5-ALA was obtained in a high yield (64%) and purity (>95%) by optimum design, which is of great potential in industrialization.

5-Aminolevulinic acid (5-ALA) is generally known as an essential precursor molecule for tetrapyrrole synthesis such as porphyrin, heme, chlorophyll and vitamin B12.¹ It has been widely applied in localizing and photodynamic therapy for various cancers.^{2–4} It has also been used as a selective biodegradable insecticide, herbicide, salt tolerance agent or plant growth regulator in agricultural fields.⁵

To date, 5-ALA was mainly synthesized by microbial production methods,⁶ but the long-time and high-cost course restrict its scaled applications. On the other side, chemical routes using 2-hydroxypyridine, tetrahydrofurfurylamine and furfurylamine as starting materials involved in numerous bottleneck including toxic intermediates and rigorous reaction conditions.^{7,8} Thus, to develop a new pathway for 5-ALA production is of great significance, especially one that is a green and sustainable.

Biomass is an appealing starting material in value-added chemicals synthesis because of its advantages of renewability, sustainability and availability.⁹ Several biomass-derived platform compounds such as 5-hydroxymethylfurfural (HMF), 5-chloromethylfurfural (CMF), levulinic acid (LA) or its esters have been reported as efficient raw materials in the production of 5-ALA.^{10,11} However, the industrial manufacture of furan-type HMF and CMF cannot currently be achieved easily due to the high production and environment costs.^{12,13} Furthermore, conversion of furan-type chemicals to 5-ALA also suffers the economic problems concerning the use of expensive oxidants in the ring-opening stage. Unlike CMF and HMF, LA and its esters can be easily produced both from hemicellulose and cellulose, and its yearly tonnage is therefore available *via* the acidic

processing of biomass at a competitively low price.^{14–16} Thus, to synthesize 5-ALA from LA or its esters is exceptionally promising. Typically, 5-ALA can be effectively prepared from levulinates *via* a three-stage process including bromination, ammoniation and acidolysis.¹⁷ However, the bromination of levulinates with Br₂ in this course has low selectivity to 5-bromo derivatives. Besides, Br₂ is hazardous and environmentally unfriendly. Hence, a crucial step of the production of 5-ALA from levulinates is to explore a safe bromide agent with higher selectivity and activity.

CuBr₂, a green and low toxic brominated reagent, was usually used for the synthesis of α -bromination of cyclopentenone derivatives and its closest analogues-indanone of carbonyl compounds for its advantages of short reaction times, high selectivity of the products, high yields and easily handle procedures.^{18,19} In this content, various unsymmetrical aliphatic ketones including levulinic acid, methyl levulinate, ethyl levulinate, 5-hydroxy-2-pentanone and 2-butanone was attempted for bromizing with CuBr₂ (Table 1). Interestingly, the yields of bromination products were different, depending on the source of aliphatic ketones.

In this work, we present the synthesis of 5-ALA from biomass derived methyl levulinate (ML) under mild conditions using CuBr₂ as a greener bromine donor, and a high yield of 5-bromo-levulinate (M5B) up to 85% was achieved. Furthermore, a detailed discussion of ammoniation and acidolysis was also presented, corresponding a high total 5-ALA yield over 64% (Scheme 1).

The first attempt to screen the reaction conditions for the bromination of ML with CuBr₂ are shown in Table 2. An encouraging yield of the desired product (50%) is indeed obtained using CuBr₂ as bromide agent in CH₃OH at 40 °C for 3 h (Table 2, entry 1). The investigation of the solvent indicated that CH₃OH–CHCl₃ mixed solvent was superior to ethyl acetate (EA), CHCl₃, CH₃OH, CH₃OH–EA and EA–CHCl₃ (Table 2, entry 2–6). The results may due to the fact that CH₃OH can improve the selectivity of M5B and haloalkanes are favourable to

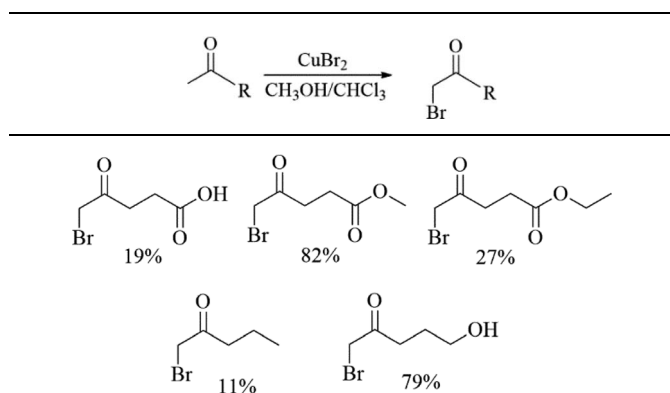
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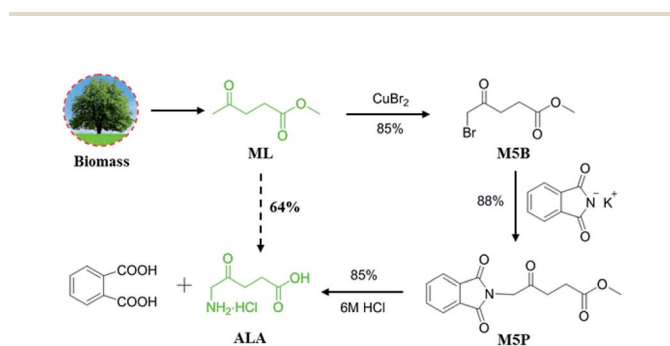
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Table 1 The bromination of aliphatic ketones with CuBr₂^a

^a Reaction condition: compounds = 2.5 mmol, CuBr₂ = 1.67 g, solvent = 30 mL, temperature = 40 °C, time = 4 h.



Scheme 1 Synthesis of 5-ALA from ML.

Table 2 The bromination of ML to M5B^a

Entry	Bromine source	Solvent	M5B yield (%)
1	CuBr ₂	CH ₃ OH	50
2	CuBr ₂	CHCl ₃	7
3	CuBr ₂	EA	13
4	CuBr ₂	CH ₃ OH/EA (1 : 1)	32
5	CuBr ₂	CHCl ₃ /EA (1 : 1)	14
6	CuBr ₂	CH ₃ OH/CHCl ₃ (1 : 1)	80
7	CuBr ₂	CH ₃ OH/CHCl ₃ (4 : 1)	56
8	CuBr ₂	CH ₃ OH/CHCl ₃ (3 : 1)	75
9	CuBr ₂	CH ₃ OH/CHCl ₃ (1 : 3)	74
10	CuBr ₂	CH ₃ OH/CHCl ₃ (1 : 4)	66
11 ^b	ZnBr ₂	CH ₃ OH/CHCl ₃ (1 : 1)	0
12 ^b	MgBr ₂	CH ₃ OH/CHCl ₃ (1 : 1)	0
13 ^b	AlBr ₃	CH ₃ OH/CHCl ₃ (1 : 1)	0
14	Br ₂	CH ₃ OH/CHCl ₃ (1 : 1)	55
15	2C ₄ H ₉ NOHBr·Br ₂	CH ₃ OH/CHCl ₃ (1 : 1)	40
16	NBS + BPO	CH ₃ OH/CHCl ₃ (1 : 1)	28
17	NBS + AIBN	CH ₃ OH/CHCl ₃ (1 : 1)	18

^a Reaction condition: ML = 0.33 g, bromine source = 3 mole of ML, solvent = 30 mL, temperature = 40 °C, time = 3 h. ^b Time = 24 h.

halogenation.^{13,20,21} Based on the above, changing the volume ratio of CH₃OH to CHCl₃ (Table 2, entry 6–10), improved the yield of M5B to 80% (Table 2, entry 6). We then proceeded to evaluate various metal bromides, including ZnBr₂, MgBr₂, and AlBr₃ under the identical conditions. However, no conversion was

detected even after 24 h (Table 2, entry 11–13). These metal bromides were also found to be inactive in bromination as noted in previous studies.^{22,23} The conventional bromination agent such as Br₂, 2C₄H₉NOHBr·Br₂ and NBS can obviously improve the reaction (Table 2, entry 14–17), although they were lower than that achieved with CuBr₂ (Table 2, entry 6). Experiments that screened for the bromine donors suggested that CuBr₂ was the most effective for the bromination of ML (Table 2, entry 6). Note that a detailed study of the reaction conditions were discussed (Tables S1, S2 and Fig. S1[†]), and a high M5B yield over 85% was obtained at 40 °C for 5 h (detected by GC-MS, Fig. S3[†]).

As shown in Fig. 1, XRD patterns indicated that CuBr₂ was transformed into CuBr (PDF#06-0292) after the reaction. When TEMPO and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were introduced to eliminate free radical, no M5B was detected. Based on these results, a mechanism for the current bromination process was proposed, as shown in Scheme 2. Initially, Lewis acidity of CuBr₂ promoted the transformation from carbonyl keto to copper-bound enolate at the α-position.²⁴ Subsequently, the hemolysis of enolate to get ethenyloxy radical, and the reactive group reacts with CuBr₂ to generate an M5B along with an equivalent of CuBr.

Intensive efforts have been devoted to introduce the key amino group on M5B.^{17,25–27} Among them, a typical Gabriel reaction using potassium phthalimide (KPI) as ammonia resource has a promising commercial availability, however, only a moderate M5P yield of 59% was achieved at 110 °C for 12 h.²⁷ In this work, optimizing the experimental conditions of Gabriel reaction including reaction time, temperature, the amount of solvent and the molar ratio of KPI to M5B (Tables S3 and S4[†]) was subsequently conducted, and a maximum M5P yield of 88% was obtained at 40 °C for only 4 h (detected by GC-MS, Fig. S4[†]). This significant improvement is no doubt accelerate the practical application of 5-ALA. Finally, an acid hydrolysis process was applied with 6 M HCl (Fig. S2[†]). The obtained products were concentrated in vacuum at 40 °C to avoid the polymerization of 5-ALA at high temperatures,¹³ affording a satisfied 5-ALA yield of 85% (Fig. S11 and 12[†]) (determined by HPLC, Fig. S5[†]).

In summary, we have developed a new efficient bromination method for the conversion of biomass derived ML to 5-ALA,

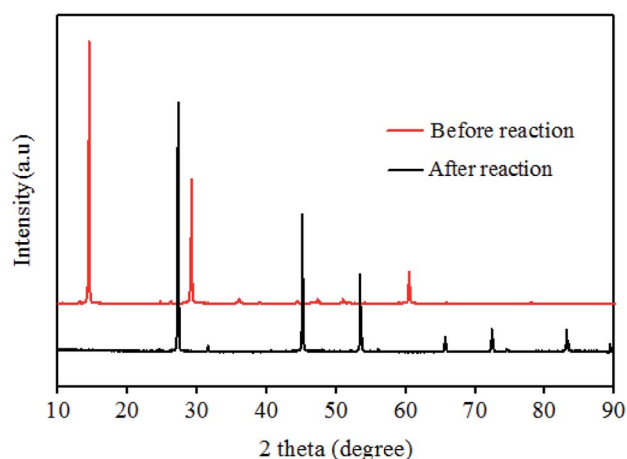
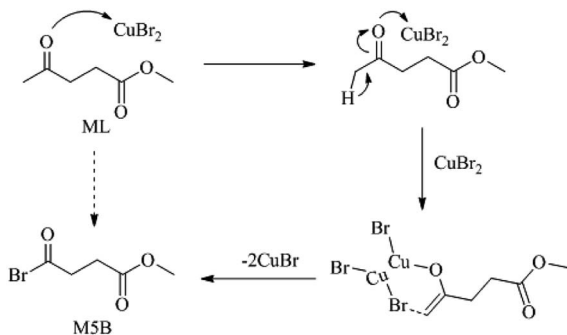


Fig. 1 XRD pattern of catalyst.





Scheme 2 The proposed mechanism of conversion of ML to M5B with CuBr_2 .

a key chemical that has been widely applied in medical and agricultural areas. CuBr_2 was applied as both catalyst and bromine atom donor and was demonstrated to be of higher selectivity and activity than the conventional hazardous Br_2 in ML bromination. Each stage proceeds in high ($\sim 85\%$) yield and affords 5-ALA in 95% purity, giving a process that could be commercially viable.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 K. Sasaki, M. Watanabe, T. Tanaka and T. Tanaka, *Appl. Microbiol. Biotechnol.*, 2002, **58**, 23–29.
- 2 M. C. Tetard, M. Vermandel, S. Mordon and J. P. Lejeune, *Photodiagn. Photodyn. Ther.*, 2014, **11**, 319–330.
- 3 T. Ishikawa, Y. Kajimoto, Y. Inoue, Y. Ikegami and T. Kuroiwa, *Adv. Cancer Res.*, 2015, **125**, 197.
- 4 H. Fukuda, A. Casas and A. Battle, *Int. J. Biochem. Cell Biol.*, 2005, **37**, 272–276.
- 5 Z. J. Zhang, H. Z. Li, W. J. Zhou, Y. Takeuchi and K. Yoneyama, *Plant Growth Regul.*, 2006, **49**, 27–34.
- 6 S. L. Liu, G. M. Zhang, X. K. Li and J. Zhang, *Appl. Microbiol. Biotechnol.*, 2014, **98**, 7349–7357.

- 7 H. Kawakami, T. Ebata and H. Matsushita, *Agric. Biol. Chem.*, 1991, **55**, 1687–1688.
- 8 H. Takeya, H. Ueki, S. Miyanari, T. Shimizu and M. Kojima, *J. Photochem. Photobiol., A*, 1996, **94**, 167–171.
- 9 A. Corma, S. Iborra and A. Velty, *Chem. Rev.*, 2007, **107**, 2411–2502.
- 10 M. Mascal and S. Dutta, *Green Chem.*, 2010, **13**, 40–41.
- 11 L. Cottier, G. Descotes, L. Eymard and K. Rapp, *Cheminform.*, 1995, 303–306.
- 12 R. J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres and J. G. de Vries, *Chem. Rev.*, 2013, **113**, 1499–1597.
- 13 M. Mascal, *ChemSusChem*, 2015, **8**, 3391–3395.
- 14 S. G. Wettstein, D. M. Alonso, E. I. Gurbuz and J. A. Dumesic, *Curr. Opin. Chem. Eng.*, 2012, **1**, 218–224.
- 15 D. M. Alonso, J. Q. Bond and J. A. Dumesic, *Green Chem.*, 2010, **12**, 1493–1513.
- 16 D. J. Hayes, S. Fitzpatrick, M. H. B. Hayes and J. R. H. Ross, *The Biofine Process – Production of Levulinic Acid, Furfural, and Formic Acid from Lignocellulosic Feedstocks*, Wiley-VCH Verlag GmbH & Co., 2008, pp. 139–164.
- 17 H. J. Ha, S. K. Lee, Y. J. Ha and J. W. Park, *Synth. Commun.*, 1994, **24**, 2557–2562.
- 18 V. Z. Shirinian, D. V. Lonshakov, V. V. Kachala, I. V. Zavarzin, A. A. Shimkin, A. G. Lvov and M. K. Mikhail, Regio- and chemoselective bromination of 2,3-diarylcyclopent-2-en-1-ones, *J. Org. Chem.*, 2012, **77**, 8112–8123.
- 19 R. H. Vekariya and H. D. Patel, Synthesis of α -bromocarbonyl compounds: recent advances, *Tetrahedron*, 2014, **70**, 3949–3961.
- 20 L. Moens, Synthesis of δ -Aminolevulinic Acid, *ACS Symp. Ser.*, 2001, **784**, 37–50.
- 21 D. R. Lane, M. Mascal and P. Stroeve, *Renewable Energy*, 2016, **85**, 994–1001.
- 22 T. Liu, J. Sun, Q. Wang, L. Li and M. D. Zhou, *Eur. J. Org. Chem.*, 2017, **2017**, 1915–1921.
- 23 M. Y. Zhou, S. S. Kong, L. Q. Zhang, M. Zhao, J. A. Duan, Z. Ou-Yang and M. Wang, *Tetrahedron Lett.*, 2013, **54**, 3962–3964.
- 24 R. W. Evans, J. R. Zbieg, S. Zhu, W. Li and D. W. C. Macmillan, *J. Am. Chem. Soc.*, 2013, **135**, 16074–16077.
- 25 L. Moens, US005907058A, Lakewood and Colo, 1999.
- 26 L. Moens, US006583317B1, Lakewood and Colo, 2003.
- 27 J. J. Bozell, L. Moens, D. C. Elliott, Y. Wang, G. G. Neuenschwander, S. W. Fitzpatrick, R. J. Bilski and J. L. Jarnefeld, *Resour., Conserv. Recycl.*, 2000, **28**, 227–239.

