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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-bromolevulinate (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

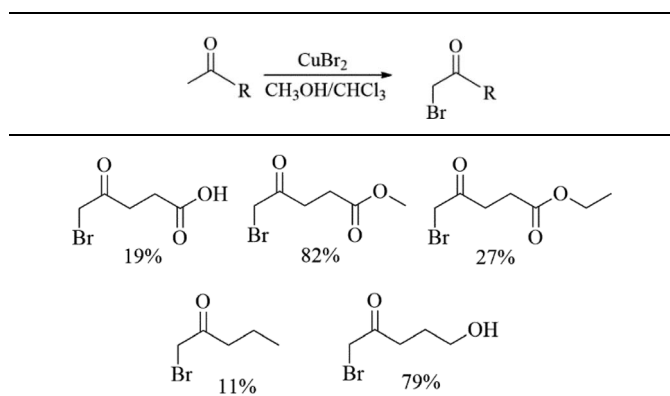
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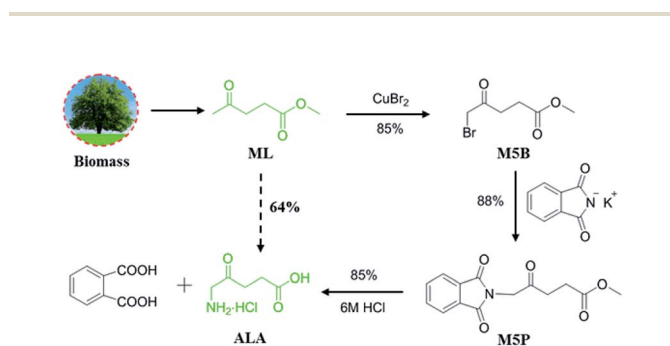
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Table 1 The bromination of aliphatic ketones with CuBr₂^a

^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,

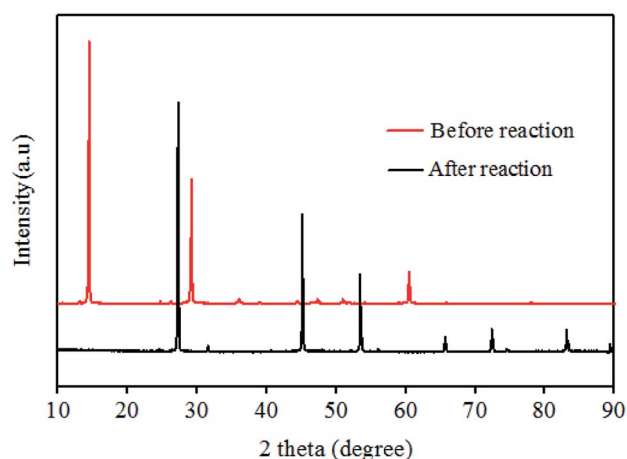
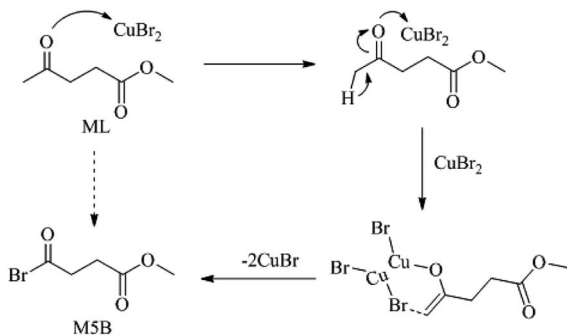


Fig. 1 XRD pattern of catalyst.





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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