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Ethyl acetate as an acetyl source and solvent for acetylation of alcohols by KOH[†]

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A KOH mediated mild, efficient, convenient and gram-scalable protocol for the acetylation of alcohols with EtOAc as acetyl source and solvent. Various types of alcohols were successfully transformed into according acetylated products. Good to excellent yields were offered by primary alcohols and low to moderate yields were offered by secondary alcohols.

In organic synthesis, aromatic esters are highly popular synthetic intermediates for chemicals and pharmaceuticals.¹ Meanwhile, acetylation could be the method of choice for protecting an alcoholic group in a complex synthetic sequence for its easy introduction, stability towards acidic reaction conditions, and mild removal by alkaline hydrolysis.² In which, acetic anhydride and acetyl chloride are the most common sources for acetylation for alcohols.³ But acetic anhydride and acetyl chloride are very unstable especially because of their high sensitivity to environmental moisture. And those acetylation reagents are usually activated in the presence of a stoichiometric quantity basic⁴ or acidic catalyst.⁵ Recently, metal triflates⁶ and other metal salts⁷ have also been reported as the catalysts for this transformation.

To comply with the principles of green synthesis, ethyl acetate (EtOAc) as acetyl source has attracted more attention, which is more environmental friendly and less-cost, ideally only producing ethanol as the by-product. Meanwhile, EtOAc with low electrophilicity. There are few reports for the esterification of alcohols by EtOAc in presence of different transition metal catalysts. The metal-based catalysts including dilithium tetratert-butylzincate (TBZL),⁸ LiClO₄/In(OTf)₃,⁹ Y₅(O¹ Pr)₁₃O,⁹ ZrCl₄-Mg(ClO₄)₂,¹⁰ CoCl₂·6H₂O,¹⁰ heterogeneous zinc/imidazole,¹¹ Zn₄(OCOCF₃)₆O,¹² InI₃/I₂,¹³ Zn reagent.¹⁴ And some transesterification of alcohols under metal-free conditions were

reported, such as Cs₂CO₃,¹⁵ I₂,¹⁶ KOtBu,¹⁷ K₂CO₃,¹⁸ Novozyme-435,¹⁹ TsOH,²⁰ (Table 1).

Although, the yield of these acetylation was satisfied, but they have obvious disadvantages such as toxicity, long reaction time, complex operation, strict reaction condition and so on. Like the procedure mediated by KOtBu which need KOtBu (1.0 mmol), DMSO (2 mL) and stirred at room temperature under argon atmosphere for 30 min. Then 1.0 mL of EtOAc was added and stirred for an additional 30 min.

Thus in spite of the recent advances, the development of a simple, mild and time efficient procedure is still of critical importance. Herein, we are reporting a short, mild and efficient acetylation methodology at room temperature with excellent yields and selectivity towards various primary alcohols.

In our initial studies, taking benzyl alcohol as the represent compound, we conducted the reactions using EtOAc as solution with KOH under room temperature. To our delight, it was clearly shown that 95% yield of desired product was obtained after only for 5 min of reaction. Based on this, we prolonged the time for 10 min, 15 min and 20 min, the yield of product was up to 99%, 97% and 95%, respectively. Then we screened other inorganic bases and observed that NaOH, LiOH could offer the desired product in a relatively lower yield. For KOtBu, NaOtBu and LiOtBu as the base, KOtBu offered a yield high to 95%. For all of the inorganic bases we screened, the Li₂CO₃ failed to carry out the reaction. Other types of organic bases, such as Et₃N and DBU, did not catalyzed this transformation. Then to find the optimum value of the amount of KOH, it was clearly shown that 97% and 95% of acetylated product was offered with 0.5 mmol and 0.25 mmol of KOH, respectively.

The reaction mechanism were similar to ref. 17 reported. The step-I is a typical acid base reaction and hence there will be an equilibrium between HO⁻ and the alkoxide as formed. The step-II is a transesterification reaction and the equilibrium depends upon stability of the alkoxide and ethoxide. Notably, the alkali metal ions plays a key role in promoting the reaction.

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Table 1 The reaction condition of previous reports on acetylation of aryl primary alcohols with EtOAc

Entry	Catalyst	Catalyst loading	Temperature/°C	Time	Solvent	Yield/%	Reference
1	TBZL	10 mol%	0	1 h	EtOAc	41	8
2	Zinc/imidazole	5 mol%	120	1 h	EtOAc	99	11
3	Zn ₄ (OCOFCF ₃) ₆ O	1.25 mol%	77–78	18 h	EtOAc	99	12
4	InI ₃ /I ₂	10 mol%/15 mol%	77–78	14 h	EtOAc	82	13
5	Zn reagent	500 mol%	rt	24 h	EtOAc	89	14
6	Cs ₂ CO ₃	15 mol%	125	1.5 h	EtOAc	81	15
7	I ₂	10 mol%	85–90	2 h	EtOAc	98	16
8	KOtBu	200 mol%	rt	20 min	DMSO	84	17
9	K ₂ CO ₃	100 mol%	77–78	1 h	EtOAc	90	18
10	Novozyme-435	5 wt%	rt	24 h	EtOAc	93	19
12	TsOH	100 mol%	rt	3 h	EtOAc	82	20
13	KOH	75 mol%	rt	10 min	EtOAc	99	This work

In this reaction, the yield was decreased as following: KOtBu > NaOtBu > LiOtBu, KOH > NaOH > LiOH, K₂CO₃ > Na₂CO₃ > Li₂CO₃. Moreover, no product was formed with organic base as the base. It indicated that the potassium ions was the best suitable ions. When the bases with potassium ions, the yield of product was ordered as KOH > KOtBu > K₂CO₃, it might be the alkalinity and alkoxide size co-effected the reaction.

Thus, the optimized reaction conditions were: substrate (0.5 mmol), KOH (0.75 mmol) and EtOAc (3 mL) were stirred at room temperature for 10 min in open air. With the optimal reaction conditions in hands, we employed various types of substrates to evaluate versatility of the procedure. At first, we tested the substrates with different substituted groups for different positions. It was clearly shown that both of the substrates with electron-donating and electron-withdrawing

group could be converted to products with high to excellent yield (Table 2, entries 1–16). And the substrates with substitute at the adjacent position on phenyl ring also gave a satisfactory yield (Table 3, entries 2, 6 and 12). The substrates containing halogen substituent also gave excellent yield of according products while no dehalogenated compounds were produced (Table 3, entries 8–12). For the substrates with various electron-withdraw group (–CF₃ or –NO₂ or –CN or –C≡C) also could be smoothly reacted under the standard condition, giving 87%, 83% and 84% yield of the desired products, respectively (Table 3, entries 13–16). In which, the –CN and –C≡C groups could be tolerated under the reaction condition. Meanwhile, primary saturated alcohols with a long chain offered high yield of products (Table 3, entries 17–20), and it noteworthy that the length of chain did not effect the acetyl procedure. For the allylic alcohols, those were converted to their corresponding products with yield high to 96%, 86% and 92%, and the C=C bond were not affected during the reaction (Table 3, entries 22–24). More important, when farnesol was scaled up to 0.5 g, the yield was still up to 85%, which indicated that this protocol has great potential for industrial applications. We also tested benzylamine and 2-benzene-methanethiol under the standard condition, unfortunately, those type of substrates cannot be reacted (Table 3, entries 25–26). And for other types of primary alcohols with heterocyclic ring, such as imidazole and thiazole cycle, which also could offer a satisficated yield (Table 3, entries 27–28). Moreover, for primary polyols, all of the OH groups were acetylated and offered a moderate yield of product (Table 3, entry 29). From the above results, it shown that this protocol could be successfully transformed various types of primary alcohols to according acetylated products in good to excellent yield.

Based on this, we initiated our studies by the catalytic acetylation of a representative substrate, 2-naphthalene-methanol, using various ester as acylating agent. Further investigation of the functionalized esters revealed that the reactivity was affected by the nature of the substituted group. These results suggest that this protocol can be applied for the acylation of alcohols with different ester.

When 2-naphthalenemethanol and methyl acetate reacted under standard condition, acetylated product was obtained in

Table 2 Optimization of reaction conditions^a

Entry	Base/mmol	T/min	Yield (%)
1	KOH/0.75	5	95
2	KOH/0.75	10	99/94^b
3	KOH/0.75	15	97
4	KOH/0.75	20	95
5	NaOH/0.75	10	75
6	LiOH/0.75	10	15
7	KOtBu/0.75	10	95
8	NaOtBu/0.75	10	84
9	LiOtBu/0.75	10	13
10	K ₂ CO ₃ /0.75	10	88
11	Na ₂ CO ₃ /0.75	10	84
12	Li ₂ CO ₃ /0.75	10	0
13	Et ₃ N/0.75	10	0
14	DBU/0.75	10	0
15	KOH/0.25	10	95
16	KOH/0.5	10	97
17	KOH/1.0	10	84

^a Substrate (0.5 mmol), base, EtOAc (3 mL), room temperature, GC yield.

^b Isolated yield.



Table 3 Acetylation of primary alcohols^a

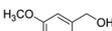
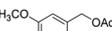
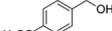
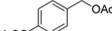
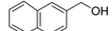
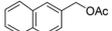
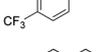
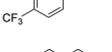
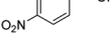
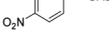
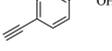
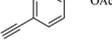
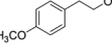
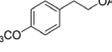
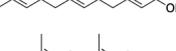
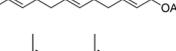
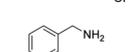
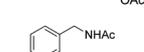
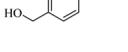
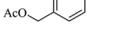
Entry	Substrate	Product/yield ^b
1		 90%
2		 92%
3		 99%
4		 92%
5		 90%
6		 93%
7		 96%
8		 96%
9		 90%
10		 93%
11		 94%
12		 87%
13		 87%
14		 83%
15		 84%
16		 91%
17		 80%
18		 85%
19		 83%
20		 86%
21		 92% ^b
22		 96%
23		 86%/85% ^c
24		 92%
25		 0%

Table 3 (Contd.)

Entry	Substrate	Product/yield ^b
26		 0%
27		 92%
28		 95%
29		 62%

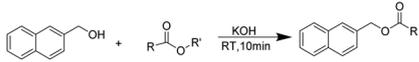
^a Substrate (0.5 mmol), KOH (0.75 mmol), EtOAc (3 mL), room temperature, 10 min, open air, isolated yield. ^b GC yield. ^c Substrate (2.25 mmol), KOH (1.69 mmol), EtOAc (15 mL).

greater than 92% yield (Table 4, entry 1). The reaction using *n*-propyl acetate (Table 4, entry 2, 94% yield), isopropyl acetate (Table 4, entry 3, 81% yield), *tert*-butyl acetate (Table 4, entry 4, 19% yield), vinyl acetate (Table 4, entry 5, 53% yield) and 2,2,2-trifluoroethyl acetate (Table 4, entry 6, 93% yield) also proceeded smoothly, in which the *tert*-butyl group, vinyl group and allyl group were clearly prevented the reverse reaction to some extent. Those results were indicated that the type of alcohol in ester affects the progress of the reaction, that is, the length of chain effected the reaction less, but the steric-effect could result in a lower yield (Table 4, entries 1–6). For the vinyl acetate as acetyl source, the product yield was lower than others, might be effected by the conjugated effect to prevent the departure of ethyleneoxy group. And for the 2,2,2-trifluoroethyl acetate, after the alkoxide attacked the carbonyl of ester, the trifluoroethoxy group was more easier to leave.

For ethyl formate as solvent, formylation product also could be obtained in high to 88% yield (Table 4, entry 7). When ethyl propionate was used, 86% yield was obtained (Table 4, entry 8). Except ethyl trifluoroacetate (0%, Table 4, entry 12), other type of esters could offer a satisfied yield of desired product. Like methyl acrylate (42% yield, Table 4, entry 9), ethyl trimethylacetate (57% yield, Table 4, entry 10), ethyl benzoate (84% yield, Table 4, entry 13) could be also as acetyl donors. From those results, it was clearly shown that the steric hindrance effect significantly affects the yield of the product (Table 4, entries 3, 4, 10 and 11). For ethyl trifluoroacetate, the ethyl trifluoroacetate offered no product, it might be due to this acetate was very easily hydrolyzed to trifluoroacetic acid, which affects the progress of the reaction. And for methyl acrylate also offered a relatively lower yield of according product, due to a by-product was produced under this condition, which was under a Michael addition of alcohols to activated alkenes promoted by KOH²¹ (Table 4, entry 9).

We further employed the screened reaction on different substituted secondary alcohols to expand the scope of the substrates. When we applied the standard condition to the 1-



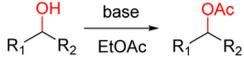
Table 4 Acylation of primary alcohols by different ester^a


Entry	Ester	Product/yield
1		92%
2		94%
3		81%
4		19%
5		53%
6		93%
7		88%
8		86%
9		42%
10		51%
11		57%
12		60%
13		0%
13		84% ^b

^a Substrate (0.5 mmol), KOH (0.375 mmol), ester (3 mL), RT, 10 min, open air, isolated yield. ^b Isolated yield.

phenylethanol, the according product was only in 14% yield. We investigated the effect of the reaction time and amount of KOH on the reaction, it observed that this reaction gave 52% yield by being stirred with 1.25 mmol KOH for 1 h (Table S1†).

Then we applied this modified reaction condition to various secondary alcohols. Compared with primary alcohols with similar substituted group, the secondary alcohols with electron rich substrates or electron deficient substrates offered the corresponding acetylated products in low to moderate yield. The

Table 5 Acetylation of secondary alcohols^a


Entry	Substrate	Product/yield
1		52% ^b
2		44%
3		33%
4		15%
5		63%
6		58%
7		53%
8		69%
9		64%
10		58%
11		57%
12		53%
13		78%
14		49%
15		51%
16		56%
17		45%
18		56%
19		32%
20		69%



Table 5 (Contd.)

Entry	Substrate	Product/yield
21		44%
22		25%
		51%
23		14%
		44%
24		0%

^a Substrate (0.5 mmol), KOH (1.25 mmol), EtOAc (3 mL), room temperature, 60 min, isolated yield. ^b GC yield.

analogues with a different length of alkyl group on its β -position of the methyl group were successfully transformed to according acetylated products in low to moderate yield. It also showed that the length of alkyl group could affect the reaction, that is, with the increasing of the alkyl group length, the yield of according product was decreased (Table 5, entries 1–3).

Meanwhile, 2-methyl-1-phenylpropanol with a steric hindrance group on the β -position was transformed into the desired product in relatively lower yield (15% yield), due to the steric hindrance effect. And for $-\text{CO}_3$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{NO}_2$ and $-\text{Cl}$ substituted analogues, the products were yielded in 63%, 58%, 53%, 69% and 64%, respectively (Table 5, entries 5–9). For 1-phenylethanol derivative with a phenyl substitute group, the reaction also could be processed (Table 5, entries 10–12). For diaryl secondary alcohols, the according product was obtained at 45–78% yield (Table 5, entries 13–17). For saturated secondary alcohols, 2-indanol and 1-phenyl-2-propanol offered 56% and 32% yield (Table 5, entries 18–19). More important, the β -O-4 dimer model compound in lignin could be converted smoothly to the acetylated product with 69% yield (Table 5, entry 20). And the β -1 model compound also offered 44% yield, which indicated this protocol might have promising application in biomass fields (Table 5, entry 21). Polyols with both primary and secondary alcohol groups, both of those group were acetylated in standard condition, offered the di-acetylated product lower than monoacetylation product (Table 5, entry 22). More important, it indicated that the primary alcohol group was more easier to be acetylated than secondary alcohol group. And we also applied this protocol to nature product, it showed that the according product was yield at 44%, indicated this methodology

had potential in medical synthesis (Table 5, entry 23). Meanwhile, the tertiary alcohol offered no product under the reaction condition, that is, the inertness towards tertiary alcohols may be attributed to steric repulsion between ethyl acetate and the hindered alcohol (Table 5, entry 24). We further tested phenols and anilines under the standard condition, but it offered no acetylated products (Table S2†). In all, while the substrate with the same substituted group, the order of reaction of reactivity of alcohols are $1^\circ > 2^\circ > 3^\circ$.

Conclusions

In conclusion, we have developed a KOH mediated mild, efficient and convenient procedure for the acetylation of alcohols with EtOAc as acetyl source and solvent in room temperature for a short time. In this process, various types of alcohols were successfully transformed into according acetylated product, and C=C bond, $-\text{CN}$, $-\text{C}\equiv\text{C}$ bond and halogen bond could be not affected under reaction condition. For those substrates, alcohols with electron rich or electron deficient substrates offered the corresponding acetylated products, in which, low to moderate yields were offered by secondary alcohols, while good to excellent yields were offered by primary alcohols. Among of them, the β -O-4 lignin dimer compound and β -1 lignin model offered the acetylated product in moderate yield. The reaction was also applicable for gram-scale synthesis. It is hopeful that this methodology is very much useful in organic synthesis and lignin transform.

Author contributions

Conceptualization, Huanjun Xu and Chunguang Lin; methodology, Xiaodan Wang, Huilin Sun and Yao Cheng; formal analysis, Xinmei Wang and Chunli Gan; investigation, Xiaodan Wang, Huilin Sun, Yao Cheng and Wenfei Yang; resources, Huanjun Xu and Jinhui Wang; writing – original draft preparation, Xiaodan Wang and Liting Xiong; writing – review and editing, Huanjun Xu and Jinhui Wang; supervision, Huanjun Xu; project administration, Huanjun Xu; funding acquisition, Huanjun Xu, Chunli Gan, Jinhui Wang and Yiyang Li. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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