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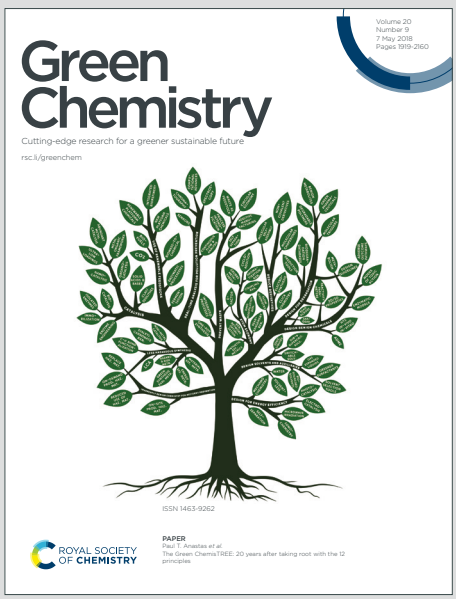

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ARTICLE

Environmentally Benign Decarboxylative N-, O-, and S-Acetylations and Acylations

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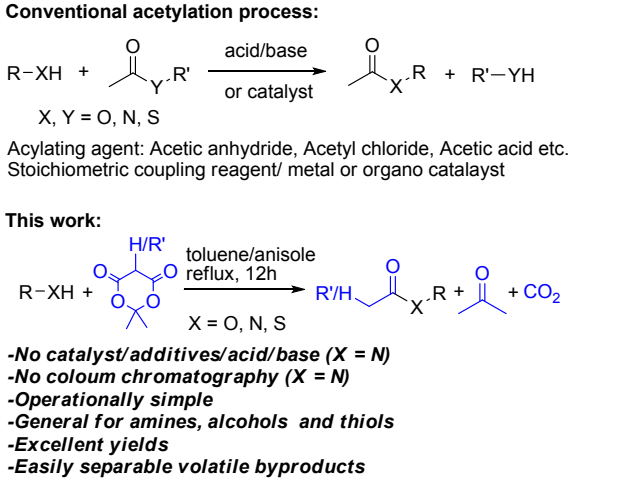
An operationally simple and general method for acetylation and acylation of a wide variety of substrates (amines, alcohols, phenols, thiols, and hydrazones) has been reported. Meldrum's acid and its derivatives have been used as an air-stable, non-volatile, cost-effective, and easy to handle acetylating/acylating agent. Easily separable byproducts (CO_2 and acetone) allowed the isolation of analytically pure acetylated products without the requirement of work-up and any chromatography.

Introduction

Acetylation is one of the most important reactions used in chemistry and biology.[1] Acetyl moiety which is frequently found in bioactive molecules, natural products, medicinal drugs, etc. is installed via acetylation reaction during their chemical synthesis. In addition, acetyl functionality is frequently used as the protecting group for the reactive functional group, such as amines, alcohols, thiols, etc. The wide application of the acetyl group prompted the development of different methods/ reagents/strategies for the acetylation reaction. The majority of acetylation reactions are carried out using acetic anhydride in the presence of an acid, a base or metal catalyst.[2] Other commonly used methodologies involve the use of acetic acid and its derivatives, such as acetyl chloride, ethyl acetate, vinyl acetate, ammonium acetate or with other acetyl sources.[3] Various metal based catalysts like zinc(II) chloride, scandium(III) triflate, bismuth(III) triflate, ruthenium(III) acetylacetonate were employed for acetylation reactions.[4] The use of CO_2 for the acetylation reaction, which generally require metal based catalyst/reagent and high-pressure of CO_2, is another important strategy.[5] The commonly used acetylating reagents are low boiling, toxic, corrosive and thus are hazardous, particularly, in the industrial scale synthesis. In addition, most of the acetylation reaction releases acids which might affect any acid-sensitive functionality that may present in the substrates. Therefore, the development of a more environmentally benign method for the acetylation reaction which operates under base or acid free conditions is essential. In this context, during our studies on the amine functionalization in the presence of Meldrum's acid, we observed an acetylation of amines. Realizing the potential of Meldrum's acid as an environmentally benign acetylating agent, we came across a seminal report by Meldrum on the synthesis of acetanilide on heating a mixture of aniline and Meldrum's acid.[6] Method for the amidation of the aniline derivative using Meldrum's acid and its derivative has also been developed recently.[7] The method works efficiently with the limited N-alkyl/aryl aniline derivative to provide the corresponding tertiary amides. However, the acylation/acetylation of primary amines such as alkylamine, benzylamines and aliphatic secondary amines involving Meldrum's acid wa s not reported. Moreover, acylation of other major functional groups such as phenol, alcohols using Meldrum's acid was not known.[8] Therefore, the development of a method that works for the acetylation of large classes of functional groups would be advantageous. Here in we report a general method for acetylation reaction that is capable of acetylating major substrate class, such as aromatic and aliphatic amines, aromatic and aliphatic alcohols, thiols, hydrazones (Scheme 1).



Scheme 1: Acetylation/acylation reactions

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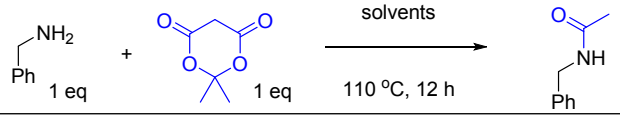
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Results and discussion

Meldrum's acid and amines are generally reacted to form the corresponding monoamides of malonic acid.[9] However, to the best of our knowledge, there is no report known for the acetylation of aliphatic amines using Meldrum's acid **2**. Therefore, our initial investigations focused on finding appropriate reaction condition for the acetylation reaction of benzylamine using Meldrum's acid (2,2-Dimethyl-1,3-dioxane-4,6-dione) **2**. Accordingly, a reaction of benzylamine and Meldrum's acid **2** was performed in refluxing toluene for 12 h. Pleasingly, analytically pure *N*-benzylacetamide (**3a**) was isolated with 90% yield without requiring any column purification (Scheme 2). Then the reactions were carried out in different other solvents in order to find better alternative of toluene (Table 1). The studies revealed that the reaction proceeded efficiently in anisole, which is categorised as "recommended" according to the solvent selection guide.[10] In addition, to minimize the quantity of solvent, the acetylation reactions with reduced amounts of solvent have also been investigated. No significant decrease in the yield of the acetylation reaction was found when the reaction was carried out with high concentration (~4 mM). Moreover, we have shown that the solvent can be recycled easily (see ESI).

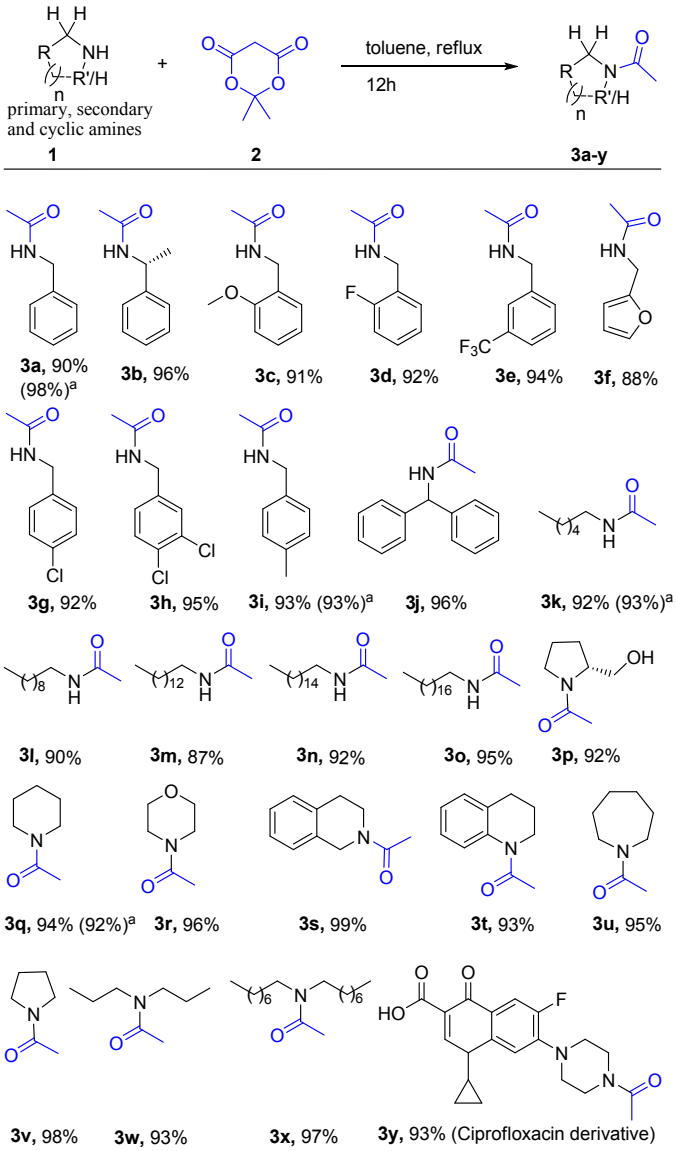
Table 1: Solvent screening for acetylation reaction.[a]



entry	solvents	yield (%)[b]
1	toluene	90
2	xylene	89
3	MIBK	93
4	cyclohexane	82
5	anisole	**98**
6	EtOAC	25
7	water	10
8[b]	water	45
9	no solvent	0
10[c]	anisole	95
11[d]	anisole	93
12[e]	anisole	94

[a]1 eq (0.93 mmol) of benzylamine was reacted with 1eq of Meldrum's acid (0.93 mmol) in 2 mL (0.47 mM) solvent. [b] TBAB (20 mol %) was used. Reaction was performed in [c]1 mL (0.93 mM), [d]0.5 mL (1.87 mM) and [e] 0.25 mL (3.72 mM) of anisole.

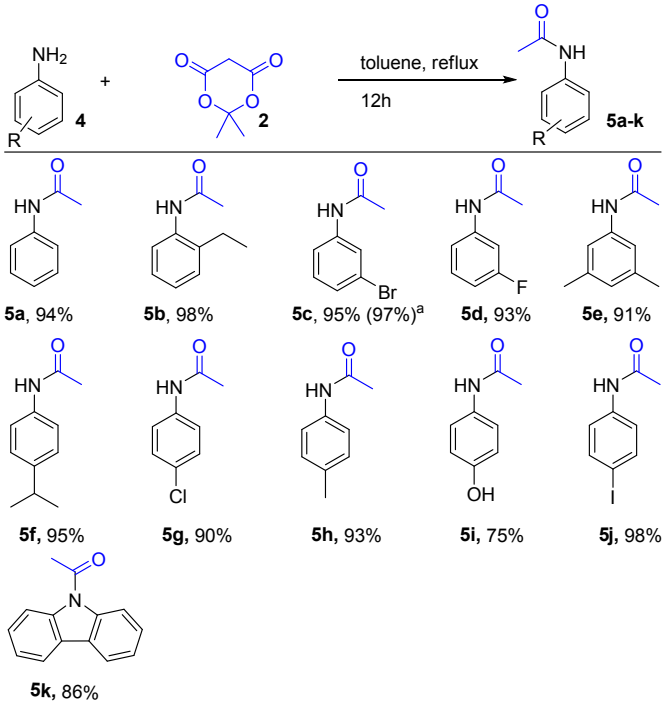
Then we became interested to investigate the substrate scope of this acetylation reaction as the desired acetylation could be achieved without the aid of any additional reagents/catalyst or additives. Moreover, the volatile byproducts acetone and carbon dioxide can be separated easily. Thus no further purification is essential to obtain the pure product. The reactions of different benzylamines with Meldrum's acid were carried out to form the acetylated products **3a**-**j** with excellent yields. In all the cases, after the completion of the reaction, the solvent was evaporated to obtain the analytically pure product. The wide range of functional groups (e.g. OMe, CF_3, Cl, F, etc.) was found to be well accepted in this reaction. Substrates having both electron donating (e.g. OMe) and electron withdrawing (e.g. F, Cl) groups were efficiently reacted to produce the desired acetylated product. Acid sensitive heteroaromatic furan ring also remained intact during the reaction to yield **3f** with very good yields. With success in the acetylation of benzylamines, we also explored acetylation of aliphatic primary amines. Different amines with variable chain lengths were reacted with Meldrum's acid **2** to obtain corresponding acetamides **3k-o** with excellent yields.



Scheme 2: Scope for the acetylation of aliphatic amine. [a]anisole was used as solvent.

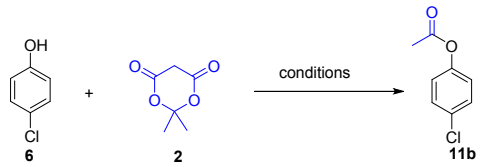
After success in the acetylation of primary amines, the acetylation reaction of secondary aliphatic amines was investigated. Accordingly, different cyclic and acyclic secondary amines were reacted with Meldrum's acid **2** under the optimized reaction conditions to afford the corresponding *N*-acylated product **3p-y** with excellent yields (Scheme-2). N-heterocycles with varied ring sizes and substituents were acetylated efficiently to obtain the desired N-acetylated heterocycles. Ciprafloxacin, an well known medicinal drug, was

also acetylated by using the standard condition to provide the N-acetyl Ciprafloxacin (**3y**) with 93% yield. The selective *N*-acetylation of (*s*)-prolinol provided the desired amide (**3p**) with very good yield. Apart form the N-heterocycles, aliphatic acyclic secondary amines also reacted smoothly with Meldrum's acid **2** to produce acetylated product with high yield (**3w** and **3x)**.



Scheme 3: Scope for the acetylation of anilines and hydrazone. [a]anisole was used as solvent.

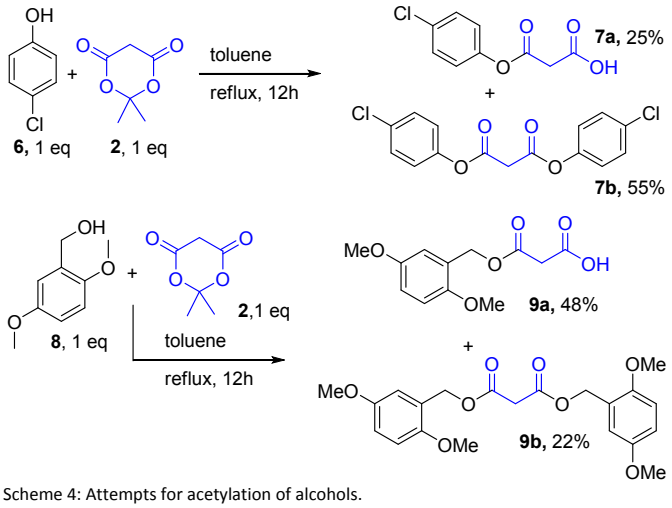
Table 2: Optimization for the acetylation of alcohol.[a]



entry	conditions	yield (%)[b]
1	toluene, reflux, 12 h	0
2	toluene, reflux, 48 h	0
3	toluene, closed tube at 120 °C, 12 h	0
4	toluene, reflux, 12 h, Et_3N (1 eq)	62
5[c]	toluene, reflux, 24 h, Et_3N (1 eq)	73
6[d]	toluene, reflux, 12 h, Et_3N (1 eq)	92
7[d]	toluene, reflux, 12 h, Et_3N (20 mol%)	92
8[d]	toluene, reflux, 12 h, DMAP (20 mol%)	72
9[d]	Anisole, 120 °C, 12 h, Et_3N (20 mol%)	95
10	anisole, 120 °C, 12 h, Et_3N (20 mol%)	74
11	anisole, 120 °C, 12 h, DIPEA (20 mol%)	76
12[e]	anisole, 120 °C, 12 h, Et_3N (5 mol%)	79
13[e]	anisole, 120 °C, 12 h, DIPEA (5 mol%)	80

[a]1 eq (0.78 mmol) of 4-chlorophenol, 1eq of Meldrum's acid (0.78 mmol), and solvent (2mL) were reacted. [b]Isolated yield. [c]1.2 eq Meldrum's acid used. [d]1.5 eq Meldrum's acid used. [e]0.25 mL of anisole was used.

With the success in acetylation of aliphatic amines, reactions using anilines were carried out to examine the generality of this method (Scheme 3). Acetylation of various anilines was performed by reacting with Meldrum's acid **2** under optimized conditions to obtain the acetanilide **5a-k** with excellent yield. The precipitated products were separated via simple filtration of the reaction mixture.

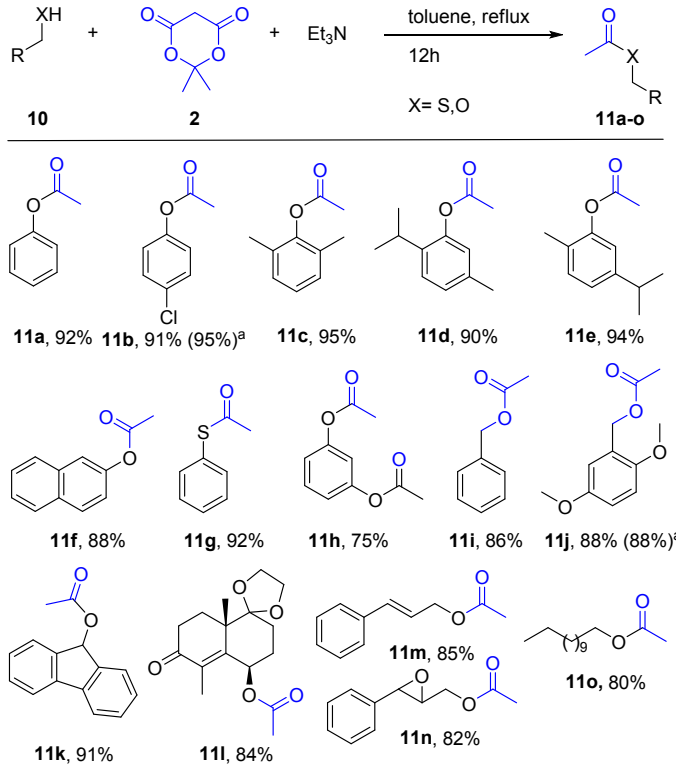


Scheme 4: Attempts for acetylation of alcohols.

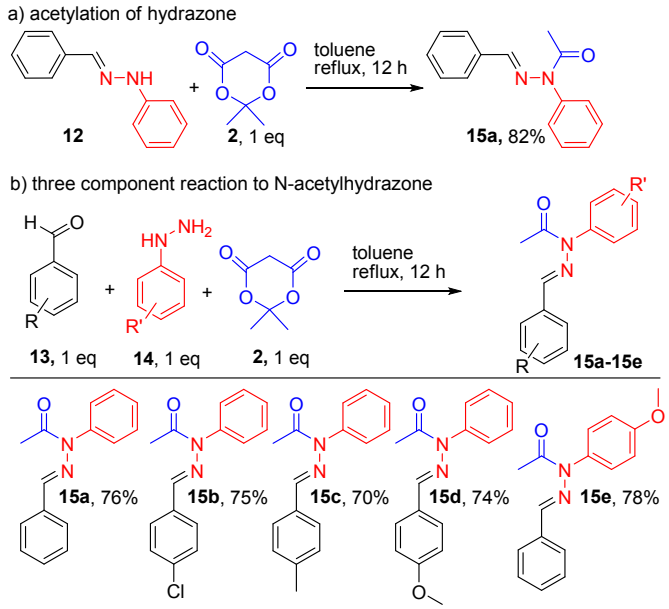
Alcohols are another potential class of substrates for acetylation. The reaction of alcohol with Meldrum's acid **2** is known to provide either the mono-ester or the di-ester of malonic acid depending on the reaction conditions.[11] We were then interested to study the scope of this acetylation reaction using alcohols as the substrates. The initial attempt by reacting para-chlorophenol **6** and Meldrum's acid **2** in refluxing toluene failed to provide the corresponding acetates **11b** (Table 2, entry 1). However, as reported previously, a mixture of mono **(7a** and **9a**) and di-ester (**7b** and **9b**) of malonic acid were formed in the reaction (Scheme 4). The reactions with increased reaction time and performing in a closed tube at 120 °C did not provide the desired product (Table 2, entry 2, 3). Then we decided to carry out the reaction in the presence of a base to facilitate decarboxylation. As anticipated, the reaction of *para*-chlorophenol **6** and Meldrum's acid **2** in the presence of triethylamine provided the desired acetate with 62% yield (Table 2, entry 4). Further increase in the yield of 92% was observed when the relative stoichiometry of Meldrum's acid **2** was increased (Table 2, entry 6). The use of a catalytic amount of base was able to provide the desired acetylation with excellent yield (92%) (Table 2, entry 7).

Phenol, benzyl alcohol, saturated aliphatic alcohols, such as dodecanol reacted smoothly to afford the desired acetates **11a-o** with excellent yield (scheme 5). Substrates bearing both electron-rich (such as 2, 6-dimethylphenol, Thymol, and Carvacol) and electron-deficient (4-chlorophenol) groups were acetylated efficiently. Cinnamyl alcohol also produced the corresponding acetylated derivatives **11m** with 85% yield. The double acetylation of resorcinol was also achieved under the same reaction conditions (**11h**). Thiophenol was also found to be an excellent substrate for this acetylation (**11g**) reaction that is employed for amines and alcohols. Acid labile groups such as

ketal (in **11l**) and epoxy functionality (in **11n**) were unaffected under these reaction conditions.

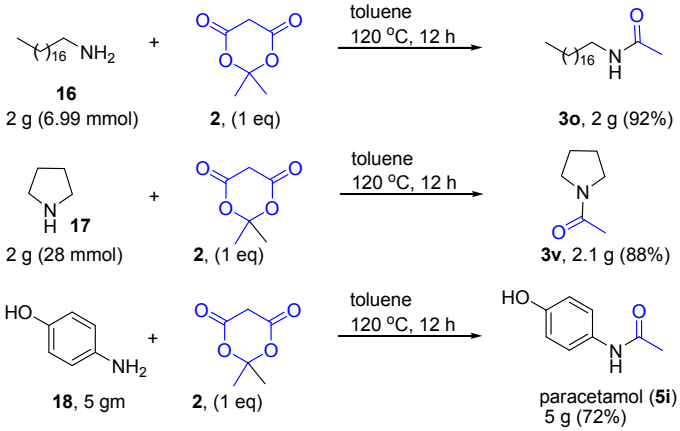


Scheme 5: Scope for the acetylation of phenols and alcohols and thiol. [a]anisole was used as solvent.



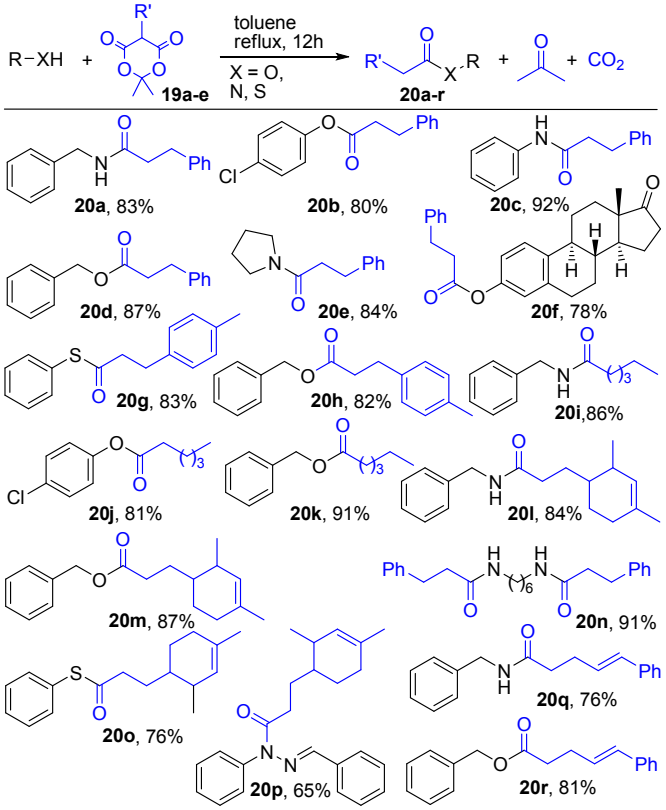
Scheme 6: Acetylation of hydrazones to N-acetylhydrazones.

N-acetylation of hydrazone was then attempted. The reaction of hydrazone **12** and Meldrum's acid **2** under standard conditions provided the desired N-acetyl derivative **15a** with very good yield (Scheme 6a). Then, the hydrazone formation and the N-acetylation of hydrazone were planned to perform in a single operation. Accordingly, aryl aldehyde, hydrazine and Meldrum's acid **2** was reacted under standard conditions. As expected, N-acetylhydrazones **15a-15e** were formed with very good yields (Scheme 6b).



Scheme 7: Preparative scale synthesis.

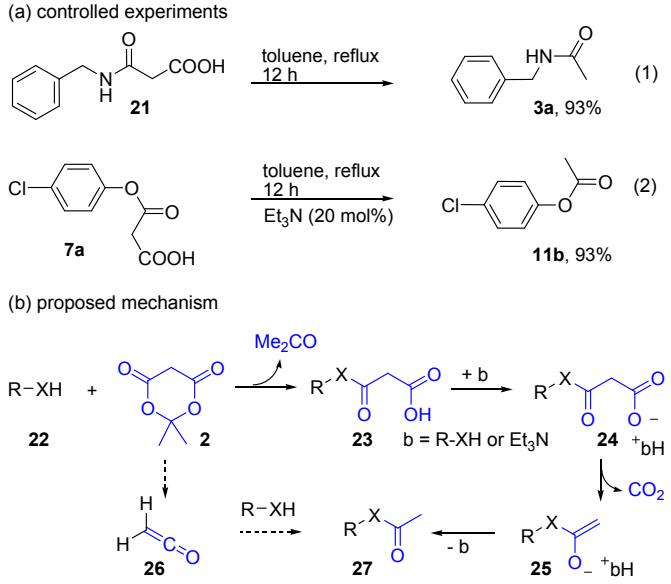
Additionally, the reaction was found to be effective in gram scale synthesis, which indicated its potential for practical application (Scheme 7). The analytically pure products (**3o** and **3v**) were obtained just after the evaporation of the solvents without involving standard work-up and column chromatography.



Scheme 8: Acylation of alcohols, amines and thiols.

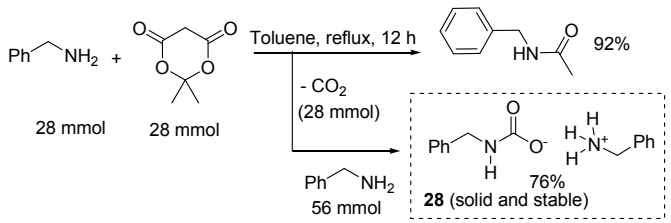
We then decided to study N-, O-, and S- acylation reactions using Meldrum's acid derivatives. Accordingly, various Meldrum's acid derivatives **19a-e** were prepared through a straight forward reductive coupling of Meldrum's acid and structurally diverse aldehyde, such as aromatic aldehyde,

aliphatic aldehyde, and vinylic aldehydes. As like acetylation reaction, a broad range of amines (aliphatic and aromatic), alcohols (aliphatic and aromatic), thiols and hydrazines participated in acylation reaction with Meldrum's acid derivatives **19a-e** to provide structurally diverse acylated products **20a**-**r** with very good to excellent yields (Scheme 8). Acylation of estrone gave the corresponding acylated estrone **20f** with very good yield. Interestingly, bis-acylation of hexamethylenediamine went smoothly to provide the corresponding bisamide **20n** with excellent yield.



Scheme 9: (a) controlled experiments. (b) Plausible mechanism for acetylation reaction.

We have performed the controlled experiments by reacting preformed mono-acid **21** and **7a** separately. Under standard reaction conditions the desired acetylated products **3a** (eq 1) and **11b** (eq 2) were isolated with excellent yields (scheme 9a). This indicates that the reaction proceeded via intermediate **23**.



Scheme 10: Trapping of CO_2.

A plausible mechanism for the acetylation reaction is shown in scheme 9b. The acetylation reaction is believed to proceed via malonic acid derivatives **23** which is formed through the reaction of nucleophilic substrates and the Meldrum's acid. Thermal decarboxylation of **24** followed by protonation of resulting enolate **25** provided the acetyl derivative **27**. The possibility of the reaction via ketene **26**, which is formed by thermal decomposition of Meldrum acid, can be eliminated as the simple reaction of alcohol and Meldrum's acid failed to provide the acetates (scheme 4). Moreover, thermal decomposition of Meldrum's acid to corresponding ketene **26** required the temperature which is higher than the current reaction temperature.[12] The isolation and identification of mono and di-ester (**7a, 9a** and **7b, 9b**) provides further support for the reaction mechanism which proceed via **23**.

Carbon dioxide which was produced during the decarboxylation of **23** was arrested efficiently as a bench–stable amine carbamate ammonium salt **28** (Scheme 10). This salt can be used as reagents and catalyst in different organic reaction.[13]

Conclusions

A generl and unprecedented method for the acetylation and acylation of amines, alcohols, thiols, and hydrazones using Meldrum's acid, which is cheap, commercially or readily available, and non-hazardous, has been developed. The volatile byproducts (CO_2 and acetone) of the reaction can be easily separated from the acetylated product without work up and column chromatography. Operational simplicity and lack of requirement of the use of additional catalyst/reagents/acid/base are the other important advantages of the present acetylation protocol.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

The acknowledgements come at the end of an article after the conclusions and before the notes and references.

Notes and references

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