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Diacyl Disulfide: A Reagent for Chemoselective Acylation of Phenols Enabled by 4-(*N*,*N*-Dimethylamino)pyridine Catalysis

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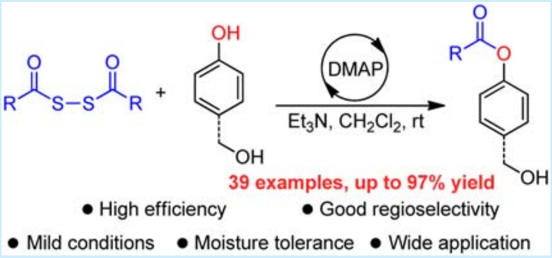
Supporting Information

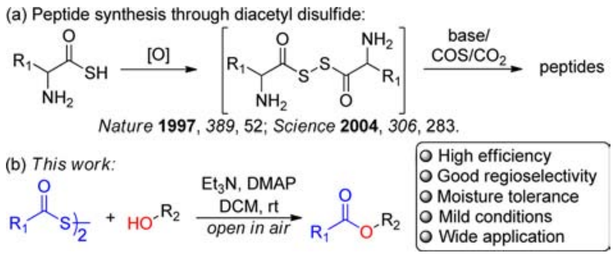
ABSTRACT: A general and excellent acylation reagent, diacyl disulfide, was uncovered for efficient ester formation enabled by DMAP (4-(*N*,*N*-dimethylamino)pyridine) catalysis. This protocol offered a promising synthetic platform on site-selective acylation of phenolic and primary aliphatic hydroxyl groups, which greatly expanded the realm of protecting group chemistry. The importance of the reagent was also reflected by its excellent moisture tolerance, high efficiency, and potential in synthetic chemistry and biologically meaningful natural product modification.



Acylation has been employed as one of the most ubiquitous and significant methodologies in the repertoire of organic synthesis, which is further reflected by intriguing implementations in medicinal and bioorganic chemistry. Equally important, it issues an important role in the protecting group chemistry, especially in terms of hydroxyl group protection.[1−3] Among all conceivable acylation reagents, acyl halide and anhydride have maximized the likelihood of their successes due to the combination of their long history and high reactivity. Nevertheless, the high reactivity of these traditional acylation reagents makes the prospects for selective acylation of polyhydroxy substrates rather bleak. Their sensitivity toward moisture also increases the difficulties of executing acylation. In this regard, an acylation reagent possessing both site-selectivity and mild operability is still deemed worthy of pursuit. Over the course of the past few decades, several kinds of reagents and auxiliaries have been developed to answer the summons, but the major issues are harsh reaction conditions, troublesome operation, as well as moisture sensitivity.[4,5]

Diacyl disulfides have been revealed as critical intermediates in the formation of oligomeric products or peptides from amino acids in prebiotic chemistry,[6,7] and most recently, they have also been proven to be efficient acylation reagents, forming amides and peptides under mild conditions in minutes to hours.[8] Despite their successes, diacyl disulfides pose distinct challenges for hydroxyl group acylation because of their excellent stability in alcohol or water even under basic conditions,[9,10] leaving many research issues for chemists to unravel. Taking inspiration from our earlier work on photoredox catalytic selective amide formation through diacyl disulfide intermediates,[8b] we anticipated that a tertiary amine such as Et_3N or DMAP used to activate the inert diacyl disulfide might also generate the highly reactive *N*-acylpyridinium ion,[11,12] thus providing an alternative protocol for selectively acylating alcohols. Herein, we report a disparate approach for selective ester bond construction enabled by novel diacyl disulfide as an efficient acylation reagent at ambient temperature (Scheme 1).

Scheme 1. Synthetic Application of Diacyl Disulfide



Seeking to realize the acylating reaction, we began to test the possibility of the in situ formation of *N*-acylpyridinium ion from tertiary amine to further access the ester bond formation. Initially, we investigated the reaction of readily accessible dibenzoyl disulfide **1**[13,14] and readily monitored phenol **2** with Et_3N as a tentative catalyst. Most gratifyingly, the desired benzoyl ester **3** was smoothly furnished in excellent yield after exposure in DCM for 9 h. In an attempt to pursue a more efficient protocol, the screening of contributing factors

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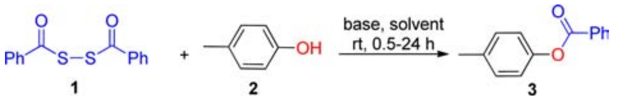
including solvents, substrate loadings, and base catalysts that might facilitate this transformation were conducted (Table 1).

Table 1. Optimization of Reaction Conditions[a]



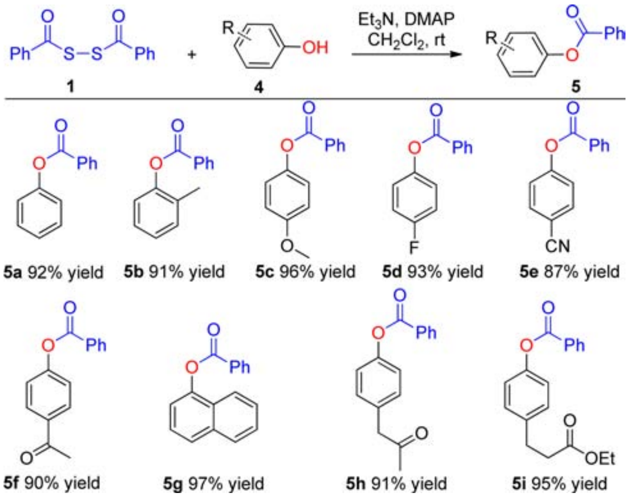
entry	solvent	base	**1** (equiv)	time (h)	yield[b] (%)
1	DCM	Et_3N	1.0	9	83
2	THF	Et_3N	1.0	12	78
3	ACN	Et_3N	1.0	12	76
4	DCE	Et_3N	1.0	9	81
5	DCM	pyridine	1.0	12	69
6	DCM	DBU	1.0	3	62
7	DCM	DMAP	1.0	0.5	96
8	DCM	K_2CO_3	1.0	9	<20
9[c]	DCM	Et_3N + DMAP	1.0	2	94
10[c]	DCM	Et_3N + DMAP	1.5	2	95

[a]Conditions: **1** (0.5 mmol), **2** (0.5 mmol), base (1.0 mmol), solvent (5.0 mL), rt. [b]Isolated yields were reported. [c]Et_3N (1.0 mmol), DMAP (0.1 mmol).

The solvent effect seemed to be rather insignificant in this process (entries 1−4), whereas the base catalyst played a deciding role in reaction efficiency (entries 5−8). Among the tested catalysts, DMAP, an acylation promoter for acyl halide and anhydride,[11,12] turned out to be the best catalyst to afford the acylation product with 96% yield in less than 0.5 h (entry 7). It merited attention that the combination of a catalytic amount of DMAP with Et_3N could also provide a satisfactory catalytic procedure without a notable decrease of yield (entry 9); thus, the practicality of the strategy was significantly enhanced. Although a slight excess of diacyl disulfide had a beneficial effect on the reaction yield and efficiency, we still decided to employ quantitative diacyl disulfide in the following reactions so as to maintain an economical protocol.

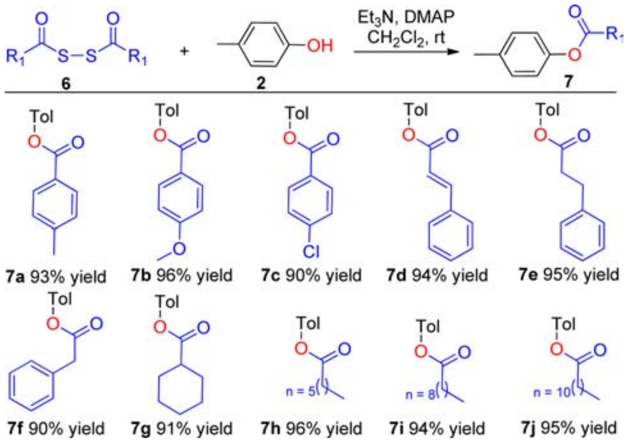
With the optimal conditions established, efforts began to evaluate the substrate scope and versatility of the DMAP-mediated acylation enabled by diacyl disulfide **1**. Therefore, various commercially available phenols **4** were tested. As compiled in Scheme 2, in each case, the desired ester products **5a−i** were isolated in excellent yields ranging from 87% to 97% in a highly efficient manner. In general, the phenols bearing electron-donating ring substituents (**5b**,**c**) tended to give slightly higher yields than those bearing electron-withdrawing ones (**5d−f**), presumably due to their beneficial nucleophilic effects. Notably, the steric hindrance of substituent on phenol **4b** showed little effect on the reactivity, delivering **5b** in higher than 90% yield. Naphthol **4g** also turned out to be a good substrate, which generated the desired naphthalenyl benzoate **5g** in 97% yield. Meanwhile, it is worth noting that this acylation approach also showed admirable functional group tolerance in the presence of benzylic ketones (**5h** and **5f**) or ester (**5i**).

Scheme 2. Substrate Scope of Phenols[a]



[a]Conditions: **1** (0.5 mmol), **4** (0.5 mmol), Et_3N (1.0 mmol), DMAP (0.1 mmol), DCM (5.0 mL), rt, 0.5−3 h. Yields of isolated products.

Scheme 3. Substrate Scope of Diacyl Disulfides[a]

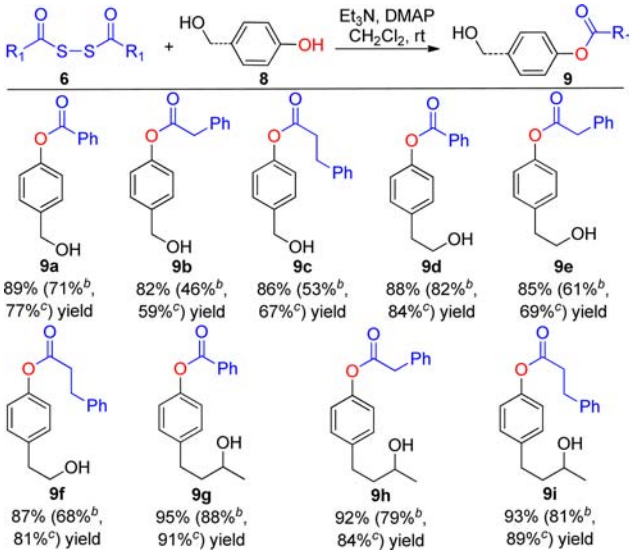


[a]Conditions: **6** (0.5 mmol), **2** (0.5 mmol), Et_3N (1.0 mmol), DMAP (0.1 mmol), DCM (5.0 mL), rt, 0.5−3 h. Yields of isolated products.

To further access the reaction scope, a range of diacyl disulfides **6**[14] were subjected to the reaction conditions, all of which successfully led to the corresponding ester products **7a−j** in excellent yields (90−96%) as shown in Scheme 3. It is worth mentioning that both the electron-donating (Me- or MeO-, **6a**,**b**) and electron-withdrawing (Cl-, **6c**) groups in diacyl disulfides were well tolerated, collectively suggesting that the electronic effects of the substituents in the aromatic ring of diacyl disulfides did not possess a similar dominating role to those of phenols **4** (Scheme 2). Moreover, substrate **6d** with an active *α*,*β*-unsaturated double bond, which pointed to a likelihood of reacting with the in situ generated disulfide intermediate through Michael addition,[15] showed no notable loss in reactivity and selectivity. Comparably, the effect of the alkyl residues of **6** was also examined, and in all cases **6e−j** cleanly afforded the desired corresponding products **7e−j** with more than 90% yields. Herein, the aforementioned remarkable results collectively lay the foundation for efficient access of acylation.

Since the alcoholic hydroxyl group is more nucleophilic than the phenolic hydroxyl motif, site-selective acylation of the latter rather than the former has attracted much attention.[16] Despite those endeavors, the current transformation is ordinarily performed under heterogeneous conditions and greatly depends on the phenolate produced in situ by strong inorganic base, usually resulting in intractable operation and frustrated yield.[17] At this stage, the central tenet of our methodology was a desire to test the behavior of diacyl disulfide, based on its notable acylation ability toward phenol. The superior selectivity toward acylation of the phenol motif to the alcoholic hydroxyl group was initially clarified in the case of 4-(hydroxymethyl)-phenol **8a**. Indeed, the corresponding phenyl monoesters **9a−c** were consistently isolated in 82−89% yields with excellent chemoselectivities (Scheme 4).[18] The influence of the aliphatic alcohol on **8** was further evaluated, and the results of 4-(2-hydroxyethyl)phenol **8b** were found to coincide with those observed previously for the substrate **8a**.[18] The phenol substrates **8c** and **8d** bearing a second alcoholic hydroxyl group turned out to be a good substrates for the reaction, leading to much better yields and selectivities (**9h,i**). Moreover, in comparison with the acyl chloride and anhydride, the diacyl disulfide tended to provide much better yield and selectivity (NMR detection seen in the Supporting Information) under similar conditions. These excellent selectivities would constitute the forefront of a mild, green synthetic process for ester formation and selective protecting group chemistry.

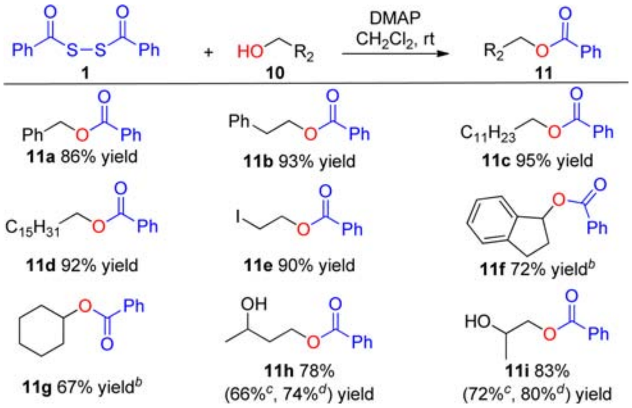
Scheme 4. Superior Acylation Selectivity of Phenol to Aliphatic Alcohol[a]



[a] Conditions: **6** (0.5 mmol), **8** (0.5 mmol), Et$_3$N (1.0 mmol), DMAP (0.1 mmol), DCM (5.0 mL), rt, 0.5−3 h. Yields of isolated products. [b] Isolated yields for acyl chlorides. [c] Isolated yields for acyl anhydrides.

Actually, our developed sequence could also be readily extended to a series of aliphatic alcohols, and the results are illustrated in Scheme 5. Although the acylation of aliphatic alcohols **10** with diacyl disulfide **6** showed less efficiency compared to the phenols, the acylation of primary alcohols **10a−e** could be generally accomplished in 3−5 h and afforded the desired products **11a−e** in good to excellent yields (86−95%) upon isolation. However, the secondary alcohols **11f,g** seemed to be troublesome substrates, and only moderate to good yields were achieved even after 12 h with 2 equiv of DMAP. This orientation was favored because the alternative secondary alcohol reaction site would encounter considerable steric congestion, providing an excellent reflection of the site-selective acylation on primary and secondary hydroxyl groups.[19] Pressing forward, substrates **10h** and **10i** were examined. Pleasingly, both well illustrated the chemoselectivity of this sequence. Thus, they significantly expanded the synthetic utility of our developed methodology.

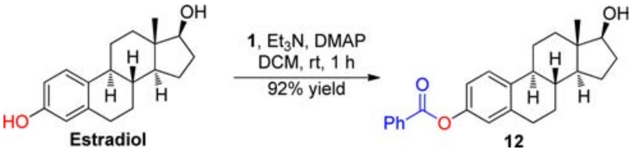
Scheme 5. Substrate Scope of Aliphatic Alcohol[a]



[a] Conditions: **10** (0.5 mmol), **1** (1.0 mmol), DMAP (2.0 mmol), DCM (5.0 mL), rt, 3−5 h. Yields of isolated products. [b] 12 h. [c] Isolated yields for acyl chlorides. [d] Isolated yields for acyl anhydrides.

The synthetic utility of diacyl disulfides could be further clarified through intelligent orchestrations with straightforward structural modification on some pharmaceutical natural products. As delineated in Scheme 6, the potent bioactive *β*-estradiol,[20] possessing both phenolic and alcoholic hydroxyl groups, served as illustrative example. Under the standard conditions, it was smoothly converted to phenyl monoester **12** in 92% yield. This representative structural elaboration demonstrated the methodology's value in providing rapid access into a focused library of a range of structural analogues bearing selectively modified functional groups.

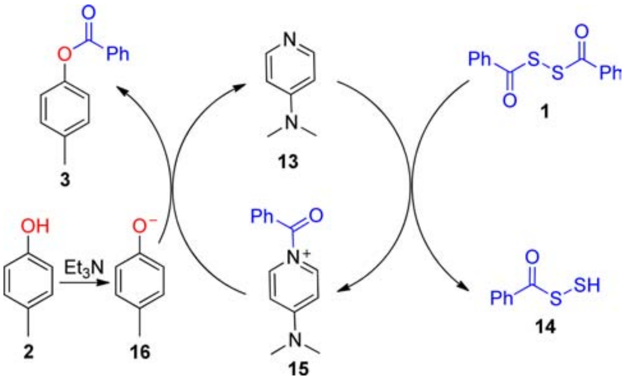
Scheme 6. Application in Natural Products Modification[a]



[a] Conditions: **1** (0.5 mmol), *β*-estradiol (0.5 mmol), Et$_3$N (1.0 mmol), DMAP (0.1 mmol), DCM (5.0 mL), rt, 1.0 h.

Undoubtedly, the mechanism of DMAP-catalyzed acylation with diacyl disulfide might possibly mirror that of acetyl anhydride.[11,12] As outlined in Scheme 7, the *N*-acylpyridinium ion **15** generated from DMAP and diacyl disulfide **1** was

Scheme 7. Proposed Mechanism of DMAP-Catalyzed Acylation with Diacyl Disulfide



considered as the key active acylation intermediate, which then reacted with the phenol anion **16** and gave the desired phenyl benzoate **3**. As a final note, the generation of phenol anion **16** was possibly the rate-determining step and played a critical role in the whole acylation sequence, given the phenol's superior reactivity toward the more nucleophilic aliphatic alcohol during the reaction process. Moreover, the acylation of primary or secondary aliphatic alcohol ought to share a similar mechanistic process with that of phenol.

In summary, diacyl disulfide was investigated as another alternatively general and excellent acylation reagent for acylating both phenolic and aliphatic alcohols apart from traditional acylation reagents acyl halide and anhydride. It was compatible with several synthetically significant functionalities and greatly expanded our understanding in the realm of protecting group chemistry. Meanwhile, this protocol offered a new synthetic platform on site-selective acylation of phenolic hydroxyl group in the presence of alcoholic one, as well as on cases of primary aliphatic hydroxyl groups in the presence of other alcoholic groups. The wide utility and potential of this strategy would be reflected in terms of its rapid access to selective protection of the hydroxyl group, pharmaceutical and agrochemical synthesis, and natural product modification as well as other synergy with strategic transformations enabled by synthetically robust diacyl disulfide. Thus, our discovery might open up new vistas for the implementation of diacyl disulfide in the repertoire of synthetic chemistry and biology.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02818.

> Experimental section, detailed experimental procedures, and full spectroscopic data for all related compounds (PDF)

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Notes

The authors declare no competing financial interest.

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