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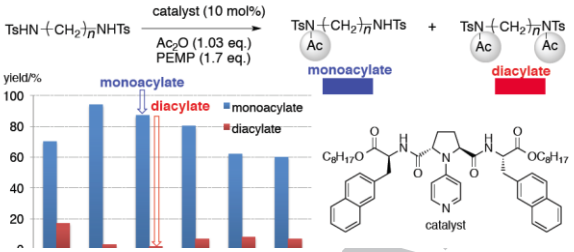

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Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

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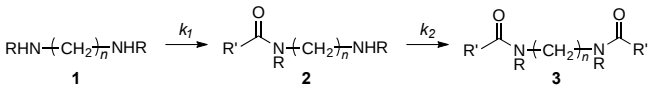
ABSTRACT

Predominant monoacylation of 1,*n*-linear disulfonamides took place in the presence of pyrrolidinopyridine-type organocatalysts when the chain length of the linear disulfonamides was n=3, 4, or 5 (monoacylate/diacylate = up to 44). The chemoselectivity of the competitive acylation between *N,N'*-ditosyl-1,5-pentanediamine (n=5) and *N,N'*-ditosyl-1,3-propanediamine (n=3) was found to be 36, favoring the former substrate. Different chain length by only one carbon atom was discriminated in the competitive acylation between *N,N'*-ditosyl-1,5-pentanediamine (n=5) and of *N,N'*-ditosyl-1,4-butanediamine (n=4) with the relative acylation rate of 16 in the presence of the organocatalyst.

Introduction

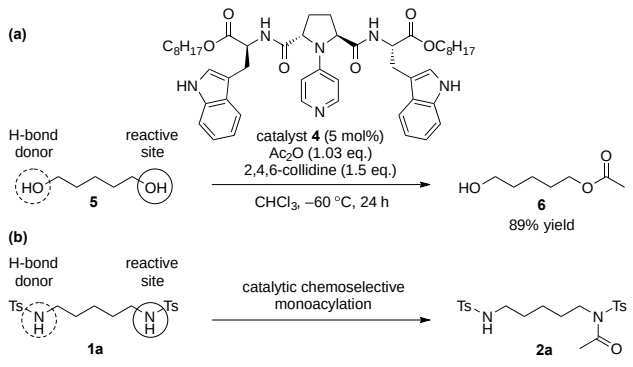
Monoacylated diamines are useful building blocks for the construction of bioactive molecules and chemical probes.[1] While selective monoacylation of symmetrical diamines is seemingly like a simple process, it has been known to be a difficult molecular transformation because overacylation is often unavoidable (Scheme 1).[2] Similar reactivity of the amino groups in diamines **1** and monoacylated diamines **2** (k_1~k_2) makes selective monoacylation difficult, especially in the case of long chain 1,*n*-linear diamines.[3] Use of large excess of diamines compared to the acyl donor is often adopted for the purpose of selective monoacylation, by minimizing the unavoidable overacylation.[4] In order to achieve selective monoacylation with only stoichiometric amount of diamine substrates, either strategy that increase k_1 (acceleration strategy) or decrease k_2 (deceleration strategy) is assumed to be feasible. Wang reported selective monobenzoylation of diamines based on the acceleration strategy employing highly reactive dianions generated with two equivalents of a strong base, *n*-BuLi.[5] Several methods based on *in situ* protection of a amino group by forming metal complexes[6] and ammonium salts[7] have been developed as the examples of the deceleration strategy. We report here selective monoacylation of 1,*n*-linear diamine derivatives (ditosylamides) through substrate recognition by organocatalysts as an additional example of the acceleration strategy.

In the course of our continuous efforts toward the development of chemo- and regioselective transformation of multi-functionalized molecules,[8] we developed chiral



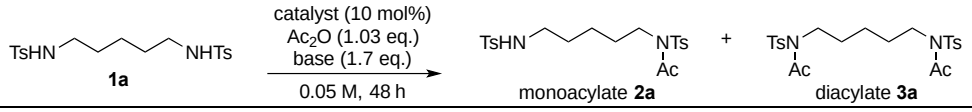
Scheme 1. Acylation of 1,*n*-linear diamines.

pyrrolidinopyridine (PPY) catalyst **4** that enables the highly chemoselective monoacylation of 1,*n*-linear diols (Scheme 2a).[9] A molecular recognition process including H-bonding interactions between the hydroxy groups of the substrates and the functional groups of the catalytic intermediate was proposed to be the origin of the highly chemoselective and accelerative monoacylation based on both experimental and computational studies.[9b] The role of the unreacting hydroxy group as a H-bond donor in the molecular recognition process was proposed to be the key for the accelerative acylation. These backgrounds prompted us to develop a method for chemoselective monoacylation of 1,*n*-linear diamine derivatives based on the molecular recognition process by the catalyst (Scheme 2b). Sulfonamide derivative **1a** with acidic NH was chosen as the substrate for monoacylation due to the expectation that the NH group would serve as an effective H-bond donor for the molecular recognition process with the catalytic intermediate.[10]

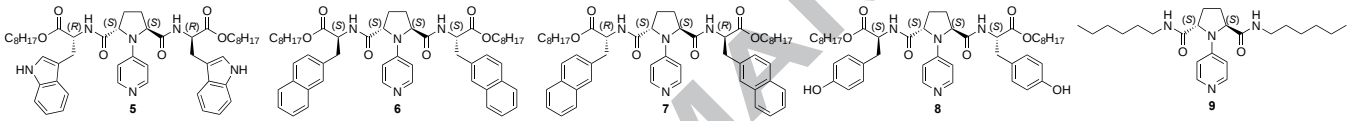


Scheme 2. Organocatalytic chemoselective monoacylation of (a) 1,5-pentanediol (previous work) and (b) *N,N'*-ditosyl-1,5-pentanediamine (this work).

Table 1. Optimization of chemoselective monoacylation of *N,N'*-ditosyl-1,5-pentanediamine **1a**



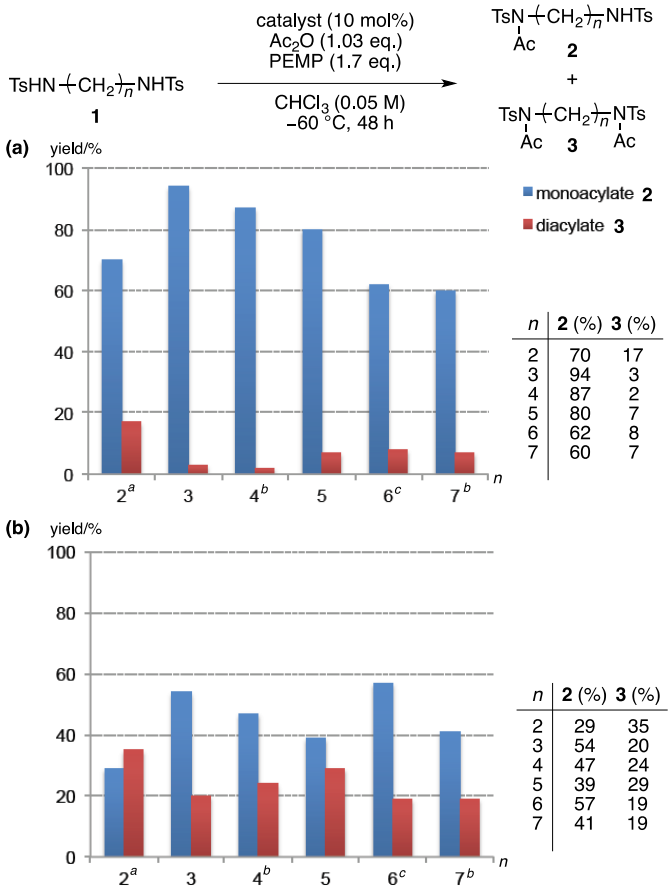
Entry	Catalyst	Base	Solvent	Temperature (°C)	Yield of **2a** (%)	Yield of **3a** (%)	S.M. recovery (%)
1	DMAP	2,4,6-collidine	$CHCl_3$	20	46	12	42
2	**4**	2,4,6-collidine	$CHCl_3$	20	34	2	60
3	**4**	2,4,6-collidine	$CHCl_3$	–60	0	0	100
4	DMAP	PEMP	$CHCl_3$	–60	39	29	30
5	**4**	PEMP	$CHCl_3$	–60	53	12	32
6	**5**	PEMP	$CHCl_3$	–60	37	10	53
7	**6**	PEMP	$CHCl_3$	–60	80	7	10
8	**7**	PEMP	$CHCl_3$	–60	46	3	47
9	**8**	PEMP	$CHCl_3$	–60	42	5	45
10	**9**	PEMP	$CHCl_3$	–60	72	12	13
11	**6**	2,4,6-collidine	$CHCl_3$	–60	0	0	100
12	**6**	PEMP	DMF	–60	8	2	90



Results and discussion

4-Dimethylaminopyridine (DMAP)-catalyzed acylation of *N,N'*-ditosyl-1,5-pentanediamine (**1a**) was first investigated as a control experiment (Table 1). Treatment of **1a** with 1.03 equiv. of acetic anhydride in the presence of 10 mol% of DMAP in $CHCl_3$ at 20 °C gave monoacylate **2a** and diacylate **3a** in 46% and 12% yield, respectively, in addition to 42% recovery of **1a** (entry 1). The reaction with catalyst **4** gave **2a** and **3a** in 34% and 2% yield, respectively, in addition to 60% recovery of **1a** (entry 2). We next run a reaction using catalyst **4** at –60 °C, expecting the higher chemoselectivity due to the more effective H-bonding interaction between the substrate and the catalyst. However, the corresponding reaction at –60 °C resulted in the complete recovery of **1a** (entry 3). We then searched for the effective auxiliary base that can promote acylation of **1a** even at –60 °C, and found that 1,2,2,6,6-pentamethylpyperidine (PEMP) is suitable for this purpose. Catalysts **4**-**9**[8] (10 mol%) with various functional side chains were examined for the selective monoacylation of **1a** at –60 °C in the presence of 1.7 equiv. of PEMP (entries 5-10). Each catalyst gave monoacylate **2a** more selectively (80/7~37/10) than DMAP (entry 4, 39/29). Chemoselectivity for the monoacylation was found to be dependent on the catalyst structure. These results suggest that the side chains of catalysts affected the chemoselectivity of the acylation between **1a** and **2a**. The best result was obtained in the acylation of **1a** with catalyst **6**[11]. Treatment of **1a** with 10 mol% of **6** in the presence of 1.7 equiv. of PEMP gave monoacylate **2a** and diacylate **3a** in 80% and 7% yield, respectively, in addition to 10% recovery of **1a** (entry 7). Use of 2,4,6-collidine as a base or DMF as a solvent under the otherwise identical conditions resulted in further poor conversion of the reaction (entries 11, 12).

The acylation of various 1,*n*-linear disulfonamides were examined (Figure 1a) under optimized conditions for monoacylation (Table 1, entry 7). For comparison, DMAP-catalyzed acylation reactions (Figure 1b) were also run under the otherwise identical reaction conditions. Highly chemoselective monoacylation of **1** (n = 3–5) took place to give the

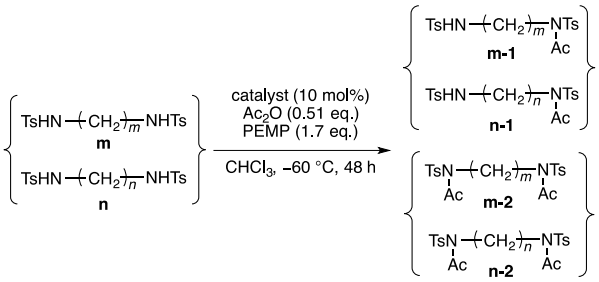


[a] Run at the substrate concentration of 0.03 M in $CHCl_3$/THF (9/1).
[b] Run at the substrate concentration of 0.025 M in $CHCl_3$.
[c] Run at 20 °C.

Figure 1. Ratios between the mono- and diacylate in the acylation of various linear diamine derivatives. (a) Acylation catalyzed by **6**. (b) Acylation catalyzed by DMAP.

corresponding monoacylate **2** in 80–94% yield with chemoselectivity (**2**/**3** = 11–44) in the presence of catalyst **6**. Moderately chemoselective monoacylation of **1** (*n* = 2, 6, 7) was observed in the presence of **6** to give the corresponding monoacylate **2** in 60–65% yield with chemoselectivity (**2**/**3** = 4–10). In contrast, random acylation of **1** took place in DMAP-catalyzed acylation, independent of the chain length of disulfonamides **1** (**2**/**3** = 0.8–3.0). The ratios of **2**/**3** observed in the DMAP-catalyzed acylation are assumed to be the result from the relative intrinsic reactivities of the disulfonamides **1** and the corresponding monoacylates **2** generated in the reaction medium. The dependence of the chain length on chemoselectivity of the monoacylation of **1** catalyzed by **6** suggests that the molecular recognition process between the catalyst **6** and disulfonamide substrates **1** may be responsible for the observed phenomena.

Table 2. Competitive acylation between different disulfonamides catalyzed by either **6** or DMAP.



Entry	*m*, *n*	Catalyst	**m**/**m-1**/**m-2**/**n**/**n-1**/**n-2**	k_m/k_n [a]
1[b]	3, 4	DMAP	29 : 50 : 10 : 70 : 16 : 3	5.0
2[b]	3, 4	**6**	11 : 88 : 0 : 85 : 10 : 0	16
3[c]	3, 5	DMAP	18 : 55 : 18 : 72 : 18 : 3	4.5
4[c]	3, 5	**6**	7 : 93 : 0 : 90 : 5 : 0	36
5[b]	4, 5	DMAP	35 : 42 : 10 : 63 : 25 : 5	2.2
6[b]	4, 5	**6**	25 : 73 : 0 : 71 : 23 : 0	4.7

[a] Determined by the following equation. Conversion was calculated from the total amount of the recovery of the two disulfonamides.

$$\frac{k_m}{k_n} = \frac{\ln\{(1-\text{conversion})\left(1-\frac{(\text{m-1+m-2})-(\text{n-1+n-2})}{(\text{m-1+m-2})+(\text{n-1+n-2})}\right)\}}{\ln\{(1-\text{conversion})\left(1+\frac{(\text{m-1+m-2})-(\text{n-1+n-2})}{(\text{m-1+m-2})+(\text{n-1+n-2})}\right)\}}$$

[b] Run at the substrate concentration of 0.025 M based on the total amount of the two sulfonamides.

[c] Run at the substrate concentration of 0.05 M based on the total amount of the two sulfonamides..

The results in Figure 1a suggest that the catalyst **6** might recognize the chain lengths of the linear disulfonamides. In order to examine this assumption, the competitive acylation reactions between two disulfonamides with different chain lengths were examined (Table 2). Treatment of a 1:1 mixture of *N*,*N'*-ditosyl-1,3-propanediamine (*m*=3) and *N*,*N'*-ditosyl-1,4-butanediamine (*n*=4) with acetic anhydride (0.51 equiv. of the total amount of two disulfonamides) in the presence of 10 mol% of DMAP gave monoacylate **m-1** in 50% yield as a major product with concomitant formation of diacylate **m-2**, monoacylate **n-1**, and diacylate **n-2** in 10%, 16%, and 3% yield, respectively, and recovery of **m** (29%) and **n** (70%) (entry 1). According to the equation shown in the footnote [a] in Table 2,[9] the relative reaction rate (k_m/k_n) was determined to be 5.0, which was assumed to correspond to the relative intrinsic reactivities between *N*,*N'*-ditosyl-1,3-propanediamine (*m*=3) and *N*,*N'*-ditosyl-1,4-butanediamine (*n*=4). On the other hand, the corresponding competitive acylation reaction catalyzed by **6** gave **m-1** highly chemoselectively in 88% yield without the formation of diacylate **m-2** and **n-2** (entry 2). The calculated relative acylation rate (k_m/k_n =16) was much larger than that (k_m/k_n =5) by DMAP. A further larger relative rate (k_m/k_n =36) was observed in the competitive acylation reaction of *N*,*N'*-ditosyl-1,3-propanediamine (*m*=3) and *N*,*N'*-ditosyl-1,5-pentanediamine (*n*=5) in the presence of catalyst **6**, whereas the corresponding relative rate catalyzed by DMAP (k_m/k_n =4.5) was comparable with that in competitive acylation reaction for *m*,*n*=3,4 (entries 1 *vs*. 3). On the other hand, much smaller relative rate (k_m/k_n =4.7) was observed in the competitive acylation between *N*,*N'*-ditosyl-1,4-butanediamine (*m*=4) and *N*,*N'*-ditosyl-1,5-pentanediamine (*n*=5) even in the presence of catalyst **6** (entry 5). These results suggests that DMAP promotes acylation depending on the intrinsic reactivity of the each of the sulfonamide substrates, whereas catalyst **6** does based on the chain-length recognition of the substrates.

In order to further examine whether the chemoselective monoacylation of the disulfonamides proceeds in an accelerative manner by hydrogen bonding interaction between the catalyst and the substrate, we chose *N*,*N'*-ditosyl-1,3-propanediamine (**10**) and as a standard substrate and compare its rate of acylation with those of the corresponding NMeTs derivative **11b** and *N*-tosyl-1,3-propanediamine (**11a**) lacking the second NHTs group (Table 3). Acylation of the NHTs derivative **10** proceeded 63 times faster than that of the corresponding NMeTs derivative **11b** in the presence of catalyst **6** (entry 4). The relative intrinsic reactivity between **10** and **11b** was estimated to be 6.4 based on the corresponding DMAP-catalyzed acylation (entry 3). The observation suggests that acylation of **10** was *ca*. 10 times more accelerated than its intrinsic reactivity in the presence of catalyst **6**. Similar phenomena were also observed in the competitive acylation between **10** and **11a**. Acylation of **10** proceeded 142 times faster than that of **11a** in the presence of catalyst **6** (entry 2). The corresponding DMAP-catalyzed competitive acylation suggested that the intrinsic reactivity of **10** was estimated to be 19 times higher than that of **11a** (entry 1). These results also imply that acylation of **10** was *ca.* 7 times more accelerated than its intrinsic reactivity in the presence of catalyst **6**. All of these results suggest that chemoselective monoacylation of **10** proceeds in an accelerative manner in the presence of catalyst **6**. The hydrogen-bonding interaction between the substrate N*H*Ts group and the catalyst is expected to be responsible for the accelerative acylation.

In conclusion, a method for the organocatalytic chemoselective monoacylation of 1,*n*-linear disulfonamides has been developed. Catalyst **6** also promoted chain-length selective monoacylation of *N*,*N'*-ditosyl-1,3-propanediamine preferentially over that of *N*,*N'*-ditosyl-1,4-butanediamine and *N*,*N'*-ditosyl-1,5-pentanediamine. Since acylsulfonamide moiety has been widely found in bioactive compounds,[12] selective modification of sulfonamide groups would become an additional tool for the development in the sulfonamide-related medicinal chemistry.

Acknowledgments

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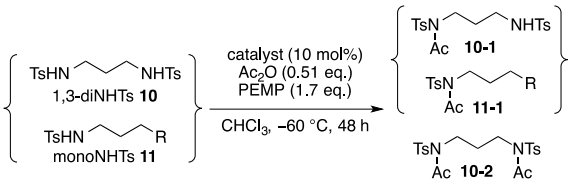
Table 3. Competitive acylation between **10** and its analogues catalyzed by either **6** or DMAP.[a]



Entry	**11**	Catalyst	**10**/**10-1**/**10-2**/**11**/**11-1**	k_{10}/k_{11}[b]
1	**11a** (R=H)	DMAP	25 : 55 : 13 : 82 : 12	19
2	**11a** (R=H)	**6**	1 : 96 : 1 : 97 : 1	142
3	**11b** (R=NMeTs)	DMAP	32 : 45 : 17 : 73 : 19	6.4
4	**11b** (R=NMeTs)	**6**	2 : 93 : 1 : 94 : 2	63

[a] Run at the substrate concentration of 0.05 M based on the total amount of the two sulfonamides.

[b] Determined by the following equation. Conversion was calculated from the total amount of the recovery of the two disulfonamides.

$$\frac{k_m}{k_n} = \frac{\ln\{(1-\text{conversion})\left(1-\frac{(\mathbf{10\text{-}1}+\mathbf{10\text{-}2})-\mathbf{11\text{-}1}}{(\mathbf{10\text{-}1}+\mathbf{10\text{-}2})+\mathbf{11\text{-}1}}\right)\}}{\ln\{(1-\text{conversion})\left(1+\frac{(\mathbf{10\text{-}1}+\mathbf{10\text{-}2})-\mathbf{11\text{-}1}}{(\mathbf{10\text{-}1}+\mathbf{10\text{-}2})+\mathbf{11\text{-}1}}\right)\}}$$

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

- An organocatalytic monoacylation of 1,n-linear disulfonamides has been developed.
- Chain-length selective acylation was observed.
- Accelerative acylation was proposed to be the origin of the selective monoacylation.