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4-Aminopyridine Catalyzed Direct and Regioselective Acylation of *N*-Tosylhydrazide

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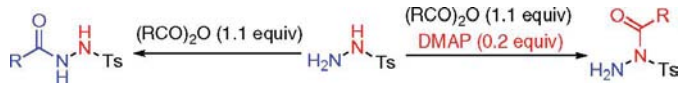
ABSTRACT



An efficient and simple method for selective acylation of either one of two nitrogen atoms of tosylhydrazide was developed. The selectivity was drastically controlled by a catalytic amount of 4-aminopyridine or 4-(dimethylamino)pyridine with common acylating agents. The nitrogen atom masked with a tosyl group was acylated in the presence of 4-aminopyridine, whereas the primary nitrogen atom was acylated in the absence of 4-aminopyridine.

Acyltosylhydrazides, which have functional importance as versatile building blocks in organic synthesis, are mostly prepared by common acylation of *N*-tosylhydrazide.[1,2] They are mainly obtained as *N*-acyl-*N*′-tosylhydrazide **1** and are widely used as a synthetic synthon for constructing aza-aromatic rings such as tetrazoles,[3] indazoles,[4] pyrazoles,[5] benzodiazepine,[6] and so on[7] and are frequently used as masked or protected functional groups that are easily converted to aldehydes,[2b,8,9] esters,[10] amides,[11] and acid chloride.[12] In particular, the conversion to aldehyde is well-known as a McFadyen−Stevens reduction.[13] In contrast, there have been very few examples of *N*,*N*-acyltosylhydrazide **2** being employed for organic synthesis,[14] although its reactivity and properties are quite interesting. One of the major obstacles to using *N*,*N*-acyltosylhydrazide **2** as a building block is its difficulty of preparation. The synthesis of related *N*,*N*-Boctosylhydrazide reported by Grehn and Ragnarsson is the first and thus far the only useful synthesis of *N*,*N*-diprotected hydrazine with two orthogonals.[15] However, the application of their method to the synthesis of *N*,*N*-acyltosylhydrazide **2** still requires cumbersome protection−

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(14) Ruwet, A.; Renson, M. *Bull. Soc. Chim. Belg.* **1966**, *75*, 157–168.
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deprotection steps. We describe herein an efficient and direct acylation of tosylhydrazide to selectively give the *N*-acyl-*N*′-tosylhydrazide **1** or *N*,*N*-acyltosylhydrazide **2** (Figure 1).

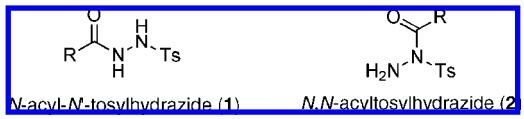
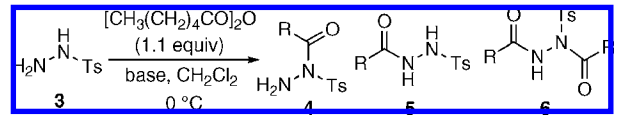


Figure 1. Acyltosylhydrazide.

In our recent synthetic study of palau'amine, we attempted a coupling of carboxylic acid with tosylhydrazide by the combined action of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI) and DMAP in dichloromethane. Surprisingly, the nitrogen atom masked with a tosyl group participated in the condensation to give a *N*,*N*-acyltosylhydrazide **2** in acceptable yield. The primary nitrogen of **2** is regarded as a nonbasic amine maintaining its nucleophilicity, and the $Hg(OTf)_2$-catalyzed direct addition of nitrogen to an alkene was achieved by using only *N*,*N*-acyltosylhydrazide **2**.[16] On the basis of this result, our effort to establish an efficient method for the preparation of *N*,*N*-acyltosylhydrazide was undertaken.

Although the origin of regioselectivity in the synthesis of **2** is not clear, the selectivity is sure to be controlled by a reagent (EDCI), a catalyst (DMAP), the substrate properties, or some combination of these factors. Therefore, to determine the effects of reagents and catayst on selectivity, tosylhydrazide **3** was just treated with 1.1 equiv of hexanoic anhydride in dichloromethane at 0 °C (Table 1). The simple reaction was completed within 90 min, and *N*-acyl-*N*′-tosylhydrazide **5** was obtained in 85% yield along with a trace amount of diacylated tosylhydrazide **6** (1%), and *N*,*N*-acyltosylhydrazide **4** was not obtained (entry 1). Presumably, the basicity of the primary amine of tosylhydrazide is not enough to be protonated by an in situ generated hexanoic acid. The same reaction in the presence of 0.2 equiv of DMAP was then conducted. Interestingly, *N*,*N*-acyltosylhydrazide **4** was obtained in an amount equal to DMAP (20%) along with **5** (15%) and **6** (33%) (entry 2). The structure of **4** was unambiguously confirmed by an X-ray diffraction study (see Supporting Information). Here, we found that DMAP plays a significant role in this selective acylation. As the DMAP seemed to be attenuated by a generating hexanoic acid, 1.5 equiv of triethylamine (TEA) therefore was employed as a base, and the reaction smoothly proceeded at 0 °C to give **4** in 90% yield (entry 3). The amout of DMAP could be reduced to 0.1 equiv without a significant loss of yield (entry 4). The reaction with triethylamine in the absence of DMAP afforded diacylated **6** as a major product, and **4** was hardly obtained (entry 5). Since monoacylated **5** possessing sulfonamide was easily converted to diacylated **6** faster than the acylation of *N*-tosylhydrazide **3** under the basic condition, the reaction using pyridine as the base was conducted. The reaction afforded **5** in 74% yield as a major product, and it was confirmed that the deprotonation of sulfonamide **5** enhanced the second acylation and that pyridine did not affect the regioselectivity as a catalyst (entry 6).

Table 1. Acylation of Tosylhydrazide with Hexanoic Anhydride



				yield (%)[a]		
entry	DMAP (equiv)	base (equiv)	time (min)	**4**	**5**	**6**
1	None	none	90		85	1
2	0.2	none	180	20	15	33
3	0.2	NEt_3 (1.5)	25	90	1	4
4	0.1	NEt_3 (1.5)	35	88	1	5
5	none	NEt_3 (1.5)	180	3	4	48
6	none	pyridine (5)	240	1	74	9

[a] NMR yield using $CHBr_3$ as an internal standard.

To clarify the effects of DMAP, the other catalysts were examined (Table 2). The commercially available 4-pyrrolydinopyridine, which has stronger nucleophilicity, accelerated the reaction, and the yield of **4** was slightly increased over that of DMAP (entry 1). Interestingly, the reaction was further accelerated by the addition of 4-aminopyridine, and **4** was obtained in 96% yield along with a trace amount of diacylated **6** (entry 2). Under these conditions, in situ generated 4-acylaminopyridine was suspected as being the actual active catalyst. Then, the prepared *N*-(pyridin-4-yl)hexanamide as a catalyst was applied to the same acylation. However, only a small amount of **4** was obtained (entry 3). The other catalysts possessing a milder nucleophilicity were also examined; 4-hydroxypyridine significantly reduced the yield of **4** (entry 4), and 4-mehoxypyridine gave almost no **4** (entry 5). The catalysts, which are not related to DMAP, were also examined. The regioselectivity was not affected by the addition of 1,4-diazabicyclo[2,2,2]octane (DABCO) as an appropriate base and 1-hydroxybenzotriazole (HOBt) as an accelerating agent of condensation (entries 4 and 5). Therefore, 4-aminopyridine was adopted as the best catalyst for the efficient preparation of *N*,*N*-acyltosylhydrazide.

With the establishment of the preparation method for *N*,*N*-acyltosylhydrazide **2**, the acylations with the other acid anhydrides were examined (Table 3). The reaction of acetic anhydride **7** with tosylhydrazide in the presence of 4-aminopyridine and triethylamine in dichloromethane at 0 °C for 30 min afforded the *N*,*N*-acetyltosylhydrazide **8** in 94% isolated yield (Table 3, entry 1). The acylation with benzoic anhydride **9** as an aromatic acid anhydride also gave the *N*,*N*-benzoyltosylhydrazide **10** in quantitative yield (entry 2). In contrast, phthalic anhydride **11**, a type of cyclic anhydride, afforded *N*-phthaloyl-*N*′-tosylhydrazide **12** in 83% NMR

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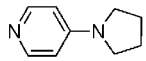
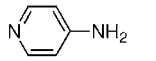
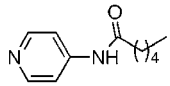
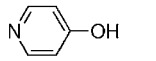
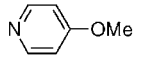
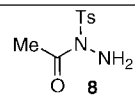
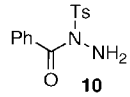
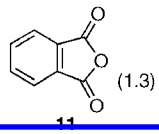
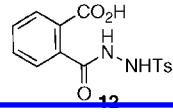
Table 2. Catalysts Related to DMAP[a]

entry	additive	time (min)	yield (%)[b] 4	5	6
1		10	92	0	8
2		5	96	0	4
3		240	6	4	43
4		120	58	2	20
5		220	5	5	46
6	DABCO	120	4	4	51
7	HOBt	120	6	5	49

[a] Conditions: H_2NNHTs (0.27 mmol), hexanoic anhydride (0.30 mmol), additive (0.05 mmol), TEA (0.41 mmol), CH_2Cl_2 (1.4 mL), 0 °C. [b] NMR yield using $CHBr_3$ as an internal standard.

yield and was purified by recrystallization in 51% yield (entry 3). The catalyst did not affect the cyclic anhydrides. It was confirmed that the selective acylation with acid anhydrides using 4-aminopyridine as a catalyst was applicable to various acid anhydrides except for a cyclic acid anhydride.

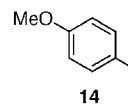
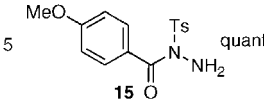
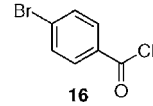
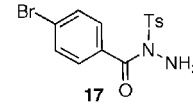
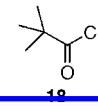
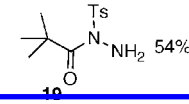
Table 3. Regioselective Acylation of Various Acid Anhydrides[a]

entry	acid anhydride (equiv)	time (h)	product (yield, %)[b]
1	Ac_2O (1.1) **7**	0.5	 **8** 94%
2	$(PhCO)_2O$ (1.5) **9**	1.5	 **10** quant
3	 (1.3) **11**	20	 **12** 51%[c] 83%[d]

[a] Conditions: H_2NNHTs (0.27 mmol), acid anhydride, 4-aminopyridine (0.05 mmol), TEA (0.41 mmol), CH_2Cl_2 (1.4 mL), 0 °C−rt. [b] Isolated yield. [c] Yield after recrystallization. [d] NMR yield using $CHBr_3$ as an internal standard.

Next, the other acylating condition was investigated to extend the regioselective acylation to more valuable carboxylic acid derivatives (Table 4). An acylation with hexanoyl chloride in the presence of 4-aminopyridine afforded **4** in 49% yield (entry 1), while **5** was obtained in 83% yield in the absence of 4-aminopyridine and TEA (entry 2). Although the yield of **4** was not sufficient, the regioselectivity was obviously controlled by 4-aminopyridine even in the acylation with acyl chloride. The reaction seemed to be stopped by the simultaneous rapid acylation of 4-aminopyridine with highly reactive acid chloride. Then, the acylation using DMAP, which has no acylation site, afforded **4** in 97% yield (entry 3). Thus, in the case of acid chloride, DMAP should be adopted in preference to 4-aminopyridine. The DMAP-catalyzed acylation with 4-methoxybenzoyl chloride **14** proceeded smoothly, and the desired *N*,*N*-(4-methoxybenzoyl)tosylhydrazide **15** was obtained in quantitative isolated yield (entry 4). In addition, even 4-bromobenzoyl chloride **16** as the aromatic acid derivative possessing an electron-withdrawing group also gave *N*,*N*-aryloyltosylhydrazide **17** in 58% yield (entry 5). The sterically bulky pivaloyl group was also able to be directly introduced to the nitrogen masked with a tosyl group, and *N*,*N*-pivaloyltosylhydrazide **19** was obtained in 54% yield (entry 6).[17] It was therefore confirmed that the selective acylation with acid chlorides using DMAP as a catalyst was also applicable to various acid chlorides.

Table 4. Selective Acylation with Various Acid Chlorides[a]

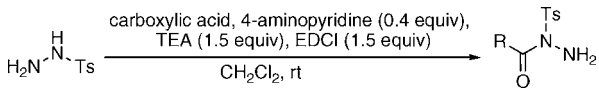
entry	acid chloride (1.3 equiv)	catalyst (0.2 equiv)	time (h)	product (yield, %)[b]
1	$CH_3(CH_2)_4COCl$ **13**	4-amino-pyridine	0.8	**4** 49%
2[c]	**13**	none	0.15	**5** 83%
3	**13**	DMAP	0.15	**4** 97%
4	 **14**	DMAP	0.15	 **15** quant
5	 **16**	DMAP	7.8	 **17** 58%
6		DMAP	5.8	 **18** 54%

[a] Conditions: H_2NNHTs (0.27 mmol), acid chloride (0.30 mmol), catalyst (0.05 mmol), TEA (0.41 mmol), CH_2Cl_2 (1.4 mL), 0 °C−rt. [b] Isolated yield. [c] TEA was not added.

Finally, the regioselective condensation of *N*-tosylhydrazide with carboxylic acids was examined (Table 5). The coupling of hexanoic acid **20** by the combined action of EDCI and 4-aminopyridine in dichloromethane afforded the desired *N*,*N*-acyltosylhydirazide **4** in 88% isolated yield (entry 1) along with a recovery of *N*-tosylhydrazide **3** (10%)

(17) The case of pyvaric anhydride and 4-aminopyridine hardly gave **19**.

Table 5. Regioselective Condensation with Various Carboxylic Acid[a]



entry	carboxylic acid	time (h)	product	yield (%)[b]
1	$CH_3(CH_2)_4COOH$ **20**	7	**4**	88
2	PhCO_2H **21**	12	Ph **22**	85
3	CO_2H **23**	4	**24**	84
4	CO_2H **25**	12	**26**	74
5	Ph O CO_2H **27**	13	Ph O **28**	77
6	MeO CO_2H **29**	4	MeO **30**	73
7	CO_2H **31**	12	**32**	76
8	CO_2H	17	**10**	21

[a] Conditions: H_2NNHTs (0.27 mmol), carboxylic acid (0.35 mmol), 4-aminopyridine (0.11 mmol), EDCI (0.41 mmol), TEA (0.54 mmol), CH_2Cl_2 (1.4 mL), rt. [b] Isolated yield (the remaining yields are almost all recovery of *N*-tosylhydrazide.

and a trace amount of diacylated tosylhydrazide **6**. In the case of the regioselective coupling with a carboxylic acid, 4-aminopyridine was slightly better than DMAP, and 0.4 equiv of 4-aminopyridine was found to be an appropriate amount.[18] Then, various carboxylic acids for the regioselective coupling were examined under these conditions. The coupling of 3-phenylpropanoic acid **21** afforded the desired *N*,*N*-(3-phenypropanoyl)tosylhydrazide **22** in 81% isolated yield (entry 2) The carboxylic acids possessing such a functional group as olefin **23**, alkyne **25**, and ether **27** and **29** also gave the corresponding desired *N*,*N*-acyltosylhydrazides, **24**, **26**, **28**, and **30** (entries 3−6, respectively) in acceptable yields. The condensation of cyclohexanecarboxylic acid **31** afforded the desired *N*,*N*-acyltosylhydrazide **32** in 76% yield (entry 7). However, only 21% of *N*,*N*-benzoyltosylhydrazides **10** was obtained by the coupling with benzoic acid **33** (entry 8), and another aromatic carboxylic acid also hardly gave *N*,*N*-aryloyltosylhydrazide. Therefore, the *N*,*N*-aryloyltosylhydrazides should be synthesized by the acylation with acid anhydride or acid chloride (Table 3, entry 2, and Table 4, entries 4 and 5).

In summary, a direct and regioselective acylation method of *N*-tosylhydrazide for the preparation of either *N*,*N*-acyltosylhydrazide or *N*-acyl-*N*′-tosylhydrazide was established. The regioselectivity was drastically controlled by the 4-aminopyridine derivatives as a catalyst, and the preparation of *N*,*N*-acyltosylhydrazide was achieved by several combinations: (i) an acid anhydride and 4-aminopyridine, (ii) a carboxylic acid, EDCI, and 4-aminopyridine, and (iii) an acid chloride and DMAP. An investigation of other applications of *N*,*N*-acyltosylhydrazide in addition to $Hg(OTf)_2$-catalyzed cyclization and the reaction mechanism that induced the regioselectivity is currently underway in our laboratory.

Acknowledgment. We thank professor Tamotsu Inabe (Hokkaido University) for the X-ray anyalysis of the *N*,*N*-acyltosylhydrazide **4**. This work was supported by the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science). K.N. is grateful to Astellas Co., Inc. for a Research Fund for Young Scientists.

Supporting Information Available: Experimental details, ^1H and ^{13}C NMR spectra of each *N*,*N*-acyltosylhydrazides and *N*-acyl-*N*′-tosylhydrazides, and data of X-ray analysis, including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The condensation reactions in the absence of 4-aminopyridine gave only a small amount of **5** and **6.**