A versatile synthon for chemoselective *N*-acylation reagents, 2-fluoro-*N*-mesylaniline

Kazuhiro Kondo, Erika Sekimoto, Kazuki Miki and Yasuoki Murakami *

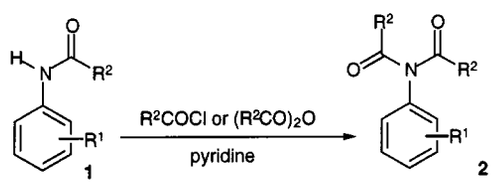
School of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan

Received (in Cambridge) 5th August 1998, Accepted 6th August 1998

2-Fluoro-*N*-mesylaniline 3b undergoes various *N*-acylations easily to give 2-fluoro-*N*-acyl-*N*-mesylanilines 4b–8b, which function as good chemoselective *N*-acylation reagents, especially for benzyloxycarbonylation.

As part of our program directed toward development of new families of acylation reagents,[1] we began to explore the chemistry of 2-substituted *N*,*N*-diacylanilines.[2] We have recently demonstrated that 2-trifluoromethyl-*N*,*N*-diacetylaniline[2a] and 2-chloro-*N*,*N*-dibenzoylaniline[2b] function as chemoselective acetylation and benzoylation reagents, respectively, for differentiating amino groups from one another. We now report that 2-fluoro-*N*-mesylaniline **3b** undergoes various *N*-acylations easily to give 2-fluoro-*N*-acyl-*N*-mesylanilines **4b**–**8b**, which function as good chemoselective *N*-acylation reagents, especially for benzyloxycarbonylation.

We first investigated the preparation of *N*,*N*-diacylanilines **2** bearing a carbamate or a bulky acyl group. As shown in Scheme 1, all attempts to prepare **2** by further acylation of *N*-acylanilines **1** did not proceed.[3] Preparation of unsymmetrical diacylanilines also proceeded unsatisfactorily.

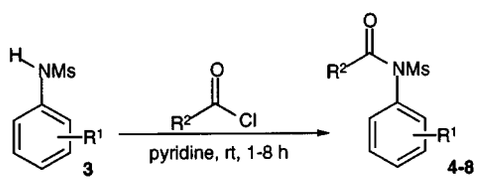


Scheme 1

We thus reasoned that *N*-mesylanilines **3** could be used to circumvent the low reactivity of *N*-acylanilines **1**, since they were expected to have lower pK_a values than **1**. After several experiments, we found that various stable *N*-acyl-*N*-mesylanilines **4**–**8** could be prepared from the corresponding aniline **3** in moderate to good yields as shown in Table 1. Among them, 2-fluoro **3b** was the best precursor for preparation of various compounds **4**–**8** (Entry 2, 6, 8, 10 and 11). In contrast, use of other *N*-mesylanilines **3c**–**e** bearing 4-fluoro, 2-methyl, and 2-chloro groups and unsubstituted **3a** gave less satisfactory results (Entry 1, 3–5, 7 and 9). Thus, we chose 2-fluoro-*N*-acyl-*N*-mesylanilines **4b**–**8b**, which were prepared in good yields from **3b** under mild conditions, as candidates for the *N*-acylation reagents. It is noteworthy in the above reactions that the introduction of a benzyloxycarbonyl group into **3b** was accomplished (Entry 2).[4]

We next turned our attention to the *N*-acyl transfer potentiality of **4b**–**8b**. Acylation of amines **9**–**12** was carried out by stirring a solution of **4b**–**8b** and amines **9**–**12** in THF. The results are shown in Table 2. All of compounds **4b**–**8b** could react as acylation reagents. Primary and secondary alkylamines, **9** and **10**, and *N*-methylbenzylamine **11** were all acylated, affording the corresponding acylated products in good yields. Sterically hindered tertiary alkyl amine **12** was not acylated even in refluxing THF. The reaction rate was greatly affected by steric bulkiness in the vicinity of the nitrogen atom in the starting amine and the acylating reagent.

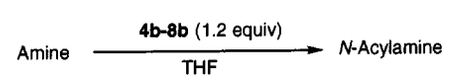
Table 1 Preparation of *N*-Acyl-*N*-mesylanilines.



Entry	R^1	R^2COCl (equiv.)	Product	Yield (%)	Recov. of **3** (%)
1	H (**3a**)	BnOCOCl (4)	**4a**	—[a]	41
2	2-F (**3b**)	BnOCOCl (4)	**4b**	90	0
3	4-F (**3c**)	BnOCOCl (4)	**4c**	39	45
4	2-Cl (**3d**)	BnOCOCl (4)	**4d**	—[a]	50
5	2-Me (**3e**)	BnOCOCl (4)	**4e**	39	49
6	2-F (**3b**)	EtOCOCl (4)	**5b**	87	trace
7	H (**3a**)	*t*-BuCOCl (4)	**6a**	29	57
8	2-F (**3b**)	*t*-BuCOCl (2)	**6b**	84	0
9	4-F (**3c**)	*t*-BuCOCl (2)	**6c**	24	69
10	2-F (**3b**)	cyclohexCOCl (2)	**7b**	91	trace
11	2-F (**3b**)	PhCOCl (2)	**8b**	92	0

[a] Formation of product **4** along with significant amounts of inseparable impurities was observed.

Table 2 Acylation potentiality of 2-fluoro-*N*-acyl-*N*-mesylaniline.



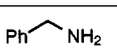
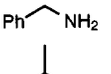
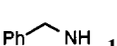
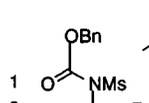
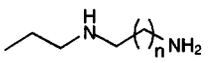
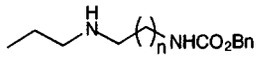
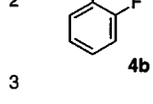
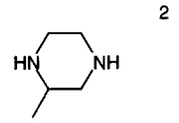
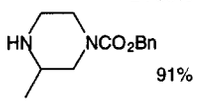
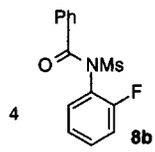
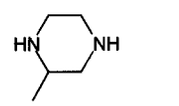
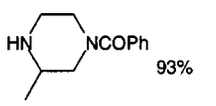
Entry	Reagent R^2	Amine	Conditions	Yield (%) of *N*-acylamine
1	BnO (**4b**)	 **9**	rt, 18 h	91
2	BnO (**4b**)	 **10**	50 °C, 24 h	90
3	BnO (**4b**)	 **11**	rt, 36 h	93
4	BnO (**4b**)	 **12**	reflux, 24 h	0
5	EtO (**5b**)	**9**	rt, 18 h	90
6	*t*-Bu (**6b**)	**9**	50 °C, 18 h	80
7	*t*-Bu (**6b**)	**10**	reflux, 24 h	77
8	cyclohex (**7b**)	**9**	40 °C, 18 h	89
9	Ph (**8b**)	**9**	rt, 2 h	93
10	Ph (**8b**)	**10**	rt, 6 h	94
11	Ph (**8b**)	**12**	reflux, 24 h	0

Table 3 Chemoselective acylation.[a]

Entry	Reagent	Diamine	Products and yields (%)
1			
		n = 1	n = 1 : 82%
2		2	2 : 86%
3			
			91%
4			
			93%

[a] All reactions were carried out with **4b** or **8b** (1.05 equiv) in THF at 0 °C for 24 h and were then left stirring at rt for 12 h.

The substantial difference in reaction rates between less hindered and hindered amines prompted us to examine the chemoselective acylation of diamines. The acylation was performed with diamines containing structurally diverse amino groups as shown in Table 3, and products acylated at the less hindered nitrogen were obtained in good yields.[5]

Our new reagents[6] **4b**–**8b** have several advantages as follows; (1) they are easily prepared from a common substrate **3b** under mild conditions, especially for benzyloxycarbonyl groups, (2) stable in air and easy to handle, (3) good selectivity: in a molecule with both less hindered and hindered amino groups, acyl transfer occurred only at the less hindered amino group.

In summary, 2-fluoro-*N*-acyl-*N*-mesylanilines **4b**–**8b** prepared easily from 2-fluoro-*N*-mesylaniline **3b**, are convenient chemoselective *N*-acylation reagents in view of their facile preparation, easy handling and stability.

Acknowledgements

This study was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, and a Sasakawa Scientific Research Grant from The Japan Science Society.

Notes and references

1 Chemoselective *N*-acylation reagents: (*a*) H. A. Staab and G. Walther, *Angew. Chem.*, 1960, **72**, 35; (*b*) T. Kunieda, T. Higuchi, Y. Abe and M. Hirobe, *Tetrahedron Lett.*, 1982, **23**, 1159; (*c*) A. Husson, R. Besselievre and H.-P. Husson, *Tetrahedron Lett.*, 1983, **24**, 1031; (*d*) T. Kunieda, T. Higuchi, Y. Abe and M. Hirobe, *Chem. Pharm. Bull.*, 1984, **32**, 2174; (*e*) A. V. Joshua and J. R. Scott, *Tetrahedron Lett.*, 1984, **25**, 5725; (*f*) Y. Nagao, K. Seno, K. Kawabata, T. Miyasaka, S. Takao and E. Fujita, *Chem. Pharm. Bull.*, 1984, **32**, 2687; (*g*) S.-I. Murahashi, T. Naota and E. Saito, *J. Am. Chem. Soc.*, 1986, **108**, 7846; (*h*) S.-I. Murahashi, T. Naota and N. Nakajima, *Chem. Lett.*, 1987, 879; (*i*) Y. Kikugawa, K. Mitsui, T. Sakamoto, M. Kawase and H. Tamiya, *Tetrahedron Lett.*, 1990, **31**, 243; (*j*) T. Keumi, M. Shimada, T. Morita and H. Kitajima, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2252; (*k*) N. Akikusa, K. Mitsui, T. Sakamoto and Y. Kikugawa, *Synthesis*, 1992, 1058; (*l*) A. R. Katritzky and H. X. Chang, *Synthesis*, 1995, **62**, 503; (*m*) M. C. O'Sullivan and D. M. Dalrymple, *Tetrahedron Lett.*, 1995, **36**, 3451; (*n*) D. Xu, K. Prasad, O. Repic and T. J. Blacklock, *Tetrahedron Lett.*, 1995, **36**, 7357; (*o*) R. S. Atkinson, E. Barker and M. J. Sutcliffe, *Chem. Commun.*, 1996, 1051; (*p*) A. R. Katritzky, B. Yang and D. Semenzin, *J. Org. Chem.*, 1997, **62**, 726; (*q*) I. S. Blagbrough and A. Geall, *Tetrahedron Lett.*, 1998, **39**, 439.

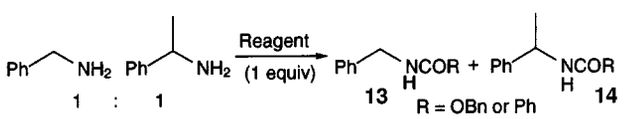
2 (*a*) Y. Murakami, K. Kondo, K. Miki, Y. Akiyama, T. Watanabe and Y. Yokoyama, *Tetrahedron Lett.*, 1997, **38**, 3751; (*b*) K. Kondo and Y. Murakami, *Chem. Pharm. Bull.*, 1998, **46**, 1217; (*c*) enantioselective *N*-acetylation: K. Kondo, T. Kurosaki and Y. Murakami, *Synlett*, 1998, 725.

3 Preparation of diacylanilines **2** with BuLi–R^2COCl (R^2 = BnO, cyclohexyl, *t*-butyl) was also unsuccessful.

4 *N*-Acetyl and benzoyl-*N*-trifluoromethanesulfonylanilines have been shown to behave as acylating reagents: J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, 1973, 4607. However, preparation of *N*-benzyloxycarbonyl-*N*-trifluoromethanesulfonylaniline was unsuccessful.

5 The selectivity in the acylation of a 1:1 mixture of a less hindered amine and a hindered amine was also investigated with **4b** and **8b**, respectively. The observed selectivity in the acylation with **4b** and **8b** was superior to the currently used reagents, as shown in Table 4 below.

Table 4 Competition acylation.



Entry	Reagent	Conditions	Yield (%) **13**+ **14**	Selectivity[a] (**13**:**14**)
1	**4b**	THF, rt, 18 h	90	8:1
2	BnOCOCl	Et_3N, THF, 0 °C, 1 h	92	3:1
3	**8b**	THF, 0 °C, 48 h	89	10:1
4	Bz_2O	THF, 0 °C, 1 h	92	5:1
5	BzCN	CH_2Cl_2, 0 °C, 12 h	97	5:1
6	Bz_2NOMe	THF, 0 °C, 12 h	88	3:1

[a] Determined by ^1H NMR analysis.

6 **Preparation of 4b:** to a stirred solution of **3b** (1.89 g, 10.0 mmol) in pyridine (25.0 mL) was gradually added ZCl (5.71 mL, 40.0 mmol) at 0 °C. The mixture was stirred for 1 h at rt. After usual work-up, purification by silica gel column chromatography (10% EtOAc in benzene) and subsequent recrystallization (benzene–hexane) afforded **4b** (2.91 g, 90%) as colorless needles, mp 97–100 °C; ν_{max}(Nujol)/cm^{-1} 1737, 1497, 1346 and 1155; $\delta_H(CDCl_3)$ 3.42 (s, 3 H), 5.21 (s, 2 H), 7.12–7.42 (m, 9 H); *m*/*z* (EI-MS) 323 (M^+), 244, 91 (bp). A satisfactory CHN analysis ± 0.3% was obtained. Other compounds **5b**–**8b** were prepared in an analogous fashion.

Communication 8/06186F