



The *ortho*-Substituted *N,N*-Diacetylaniline as a Selective Acetylating Reagent.

Yasuoki Murakami*, Kazuhiro Kondo, Kazuki Miki,
Yoko Akiyama, Toshiko Watanabe, Yuusaku Yokoyama

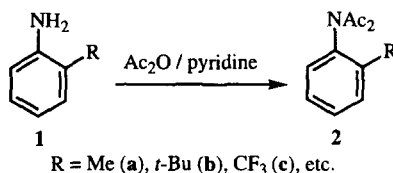
School of Pharmaceutical Sciences, Toho University,

2-2-1 Miyama, Funabashi, Chiba 274, Japan

Abstract : Selective acetylation of the less hindered amino group in the presence of the more hindered amino group with the use of 2-trifluoromethyl-*N,N*-diacetylaniline **2c** is described. This acetylation with **2c** yielded the corresponding less hindered monoacetamide exclusively, simply, conveniently, and in good yields. © 1997 Elsevier Science Ltd.


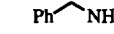


ortho- (or 2-) Substituted anilines **1** undergo *N,N*-diacetylation more easily than *ortho*-unsubstituted ones (Scheme 1).¹⁾ On the basis of our study^{1c-e)} on the *N,N*-diacetylation of *ortho*-substituted anilines **1**, we planned to explore the potential applications of the *ortho*-substituted *N,N*-diacetylanilines **2** in acetylation reaction. The imide character of the *N,N*-diacetylanilines **2**, which were easily prepared from the corresponding *ortho*-substituted anilines **1**, was expected to serve as a good acetylating reagent to nucleophiles. Acetylation of amines is one of the most fundamental transformations in organic chemistry,²⁾ and selective acetylation of the less hindered amino group in polyamines is often required. Several reagents have been developed for the above purpose.³⁻¹¹⁾ In this paper we wish to describe a simple but powerful reagent for selective acetylation in a series of structurally diverse diamines.

Scheme 1



We first investigated the acetylating potentiality of various *N,N*-diacetylanilines **2a-c** with the effect of solvents. All of them could react as an acetylating reagent as shown in Table 1. 2-Trifluoromethyl-*N,N*-diacetylaniline **2c** was the most effective reagent (Table 1, Entry 1-3). Any of the solvents (EtOH, DMF, MeCN, THF, and CH₂Cl₂) was suitable for the reaction (Table 1, Entry 3-7). The diacetylaniline **2c** was effective for not only primary but also *N*-methyl and secondary amines (Table 1, Entry 8, 9). Sterically hindered cumylamine (**6**) and aniline (**7**) were also acetylated under reflux (Table 1, Entry 10, 11).

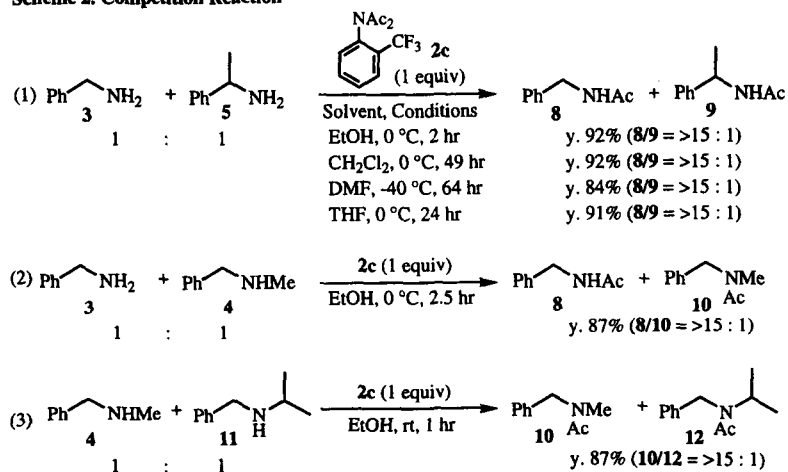
Table 1. *N*-Acetylation of Various Amines Using the *N,N*-Diacetylanilines 2a-c

Entry	Amine	R	Solvent	Conditions	Yield (%)
1		Me (2a)	EtOH	rt, 4 h	97
2		<i>t</i> -Bu (2b)	EtOH	reflux, 3 h	54
3	 3	CF ₃ (2c)	EtOH	rt, 3 h	99
4		CF ₃	DMF	rt, 3 h	97
5		CF ₃	MeCN	rt, 12 h	95
6		CF ₃	THF	rt, 12 h	95
7		CF ₃	CH ₂ Cl ₂	rt, 8 h	94
8	 4	CF ₃	EtOH	rt, 6 h	99
9	 5	CF ₃	EtOH	rt, 6 h	98
10 ¹⁾	 6	CF ₃	EtOH	reflux, 24 h	88
11 ²⁾	Ph-NH ₂ 7	CF ₃	EtOH	reflux, 24 h	98

1) The reagent 2c (2 equiv) was used. 2) The reagent 2c (4 equiv) was used.

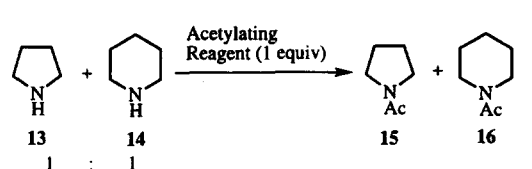
The substantial difference in reaction rates between hindered and less hindered amines prompted us to examine selective acetylation of amines. We chose to investigate the selectivity in the acetylation of a 1 : 1 mixture of a hindered amine and a less hindered amine with the diacetylaniline 2c. The results are summarized in Scheme 2.^{12, 13} In all cases, high selectivity was observed.^{14, 15}

Scheme 2. Competition Reaction



In order to demonstrate the highly selective acetylation of our diacetylaniline **2c**, two other reagents, *N*-acetyl-*N*-acyl-3-aminoquinazoline¹⁰ **17** and *N*-methoxydiacetamide⁹ **18**, were compared with **2c** for competitive acetylation. The results are summarized in Table 2. Taking the experimental results independently reached by the Atkinson group and ours into consideration, we could conclude that the diacetylaniline **2c** was the most effective reagent. We wish to add that the diacetylaniline **2c** can be easily prepared from commercially available 2-trifluoromethylaniline **1c** in one step and is readily handled in air.^{16,17})

Table 2. Comparison with Other Reagents

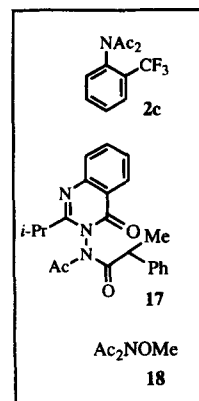


Entry	Reagent	Yield (%)	Selectivity (15 : 16)
1 ¹⁾	2c	70	>15 : 1 ²⁾
2	17	- ³⁾	8 : 1
3	18	- ³⁾	3 : 1

1) The acetylation was carried out in EtOH-THF-DMF (2:2:1) for 48 h at -60 °C. Solvent was chosen for solubility.

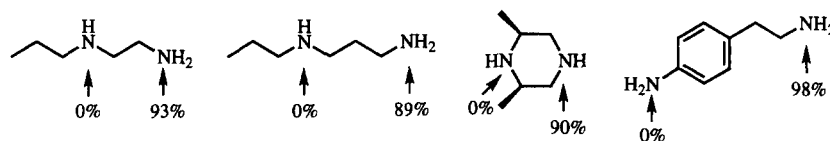
2) The ratio was determined by ¹H NMR (400 MHz) analysis.

3) No yield was reported by Atkinson *et al.*



In order to explore the generality and scope of the above selective acetylation by the diacetylaniline **2c**, the acetylation was examined with various structurally diverse amines. The results are shown in Figure 1. In all cases, the reactions proceeded cleanly, and the less hindered acetylated products were obtained in high yields.¹⁸⁾

Figure 1. Selective Acetylation Using the Diacetylaniline **2c**



All reactions were carried out with **2c** (1.2 equiv) in EtOH at 0 °C.

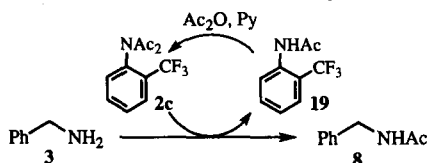
In summary, 2-(2,2,2-trifluoromethyl)-*N,N*-diacetylaniline **2c** has been found to be an effective reagent in selective acetylation for differentiating amino groups from one another. Work on other synthetic reactions using the reagent **2c** is now in progress.

ACKNOWLEDGMENT

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12. The acetylation (Scheme 2, eq 1) using Ac₂O (Et₃N, CH₂Cl₂, 0 °C, 2 h) gave no selectivity (**8** : **9** = 1 : 1).
13. Slow acetylation (12 h) occurred with 2-methyl-*N,N*-diacetylaniline **2a**, but gave satisfactory results (87% yield, *N*-acetylbenzylamine **8** : *N*-acetyl-*N*-methylbenzylamine **10** = >15 : 1).
14. The ratio was determined by ¹H NMR (400 MHz) analysis.
15. The acetylation (Scheme 2, eq 1) using Kunieda's reagent⁴⁾ (1 equiv) gave *N*-acetylbenzylamine **8** in lower yield (60-65%) than ours with similar selectivity.
16. The acetanilide **19** can be recovered in >95% yield and recycled by acetylation (see ref. 17).



17. 2-Trifluoromethyl-*N,N*-diacetylaniline **2c** was prepared as published previously (see ref. 1e). The reaction conditions were slightly modified in this paper and the yield increased to 90% from 46%.
Preparation of **2c**: To a stirred solution of 2-trifluoromethylaniline **1c** (4.81 g, 29.9 mmol) in pyridine (60.0 mL) was added Ac₂O (22.5 mL, 224 mmol) at 0 °C. The reaction mixture was stirred at 100 °C for 12 h, allowed to cool, and concentrated. The residue was purified by silica gel column (20%EtOAc in benzene) to give **2c** (90%, 6.60 g) as a colorless solid. This reagent **2c** can be stored at rt under air for a few years without decomposition.
18. The representative experimental procedure for selective acetylation is as follows: To a stirred solution of *N*-propylethylenediamine (75.0 μL, 0.612 mmol) in EtOH (2.0 mL) was added 2-trifluoromethyl-*N,N*-diacetylaniline **2c** (165 mg, 0.673 mmol) at 0 °C. The reaction mixture was stirred at the same temperature until the reaction was completed (12 h), and concentrated. The crude product was purified by silica gel* column (50% MeOH in CHCl₃) to give *N*-acetyl-*N'*-propylethylenediamine (93%, 82.1 mg) as a colorless solid. *NH-type silica gel chromatorex NHDM1020[®] purchased from Fuji Silysia Chemical Ltd.

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