

2-Chloro-*N,N*-dibenzoylaniline: a Selective *N*-Benzoylating Reagent

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Highly selective benzoylation of a less hindered amino group in the presence of a more hindered amino group with 2-chloro-*N,N*-dibenzoylaniline (**2d**), a convenient to use and stable reagent, is described.

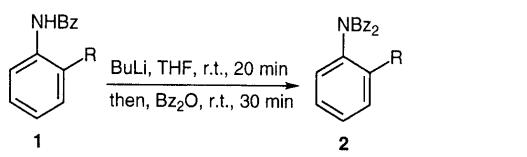
Key words *ortho*-substituted aniline; diacylaniline; 2-chloro-*N,N*-dibenzoylaniline; imide; selective *N*-benzoylation

N-Benzoylation is important for the protection of amines in organic and bioorganic synthesis,¹⁾ and selective benzoylation of a less hindered amino group in polyamines is often required. Several reagents have been developed for the above purpose.²⁻⁶⁾ However, the conventional reagents are still unsatisfactory in terms of broad usefulness or selectivity. As part of a program directed toward the development of new families of acylating reagents, we have begun to explore the chemistry of *ortho*- (or 2-) substituted *N,N*-diacylanilines.⁷⁾ In this paper, we wish to report that 2-chloro-*N,N*-dibenzoylaniline (**2d**) serves as an efficient reagent in the selective benzoylation of a less hindered amino group in the presence of a more hindered amino group.

The *N,N*-dibenzoylanilines **2** were readily prepared in good yields from the corresponding *N*-benzoylanilines **1** with BuLi-benzoic anhydride (Bz_2O) in tetrahydrofuran (THF) (Table 1).^{8,9)} After purification, the solid products **2** can be stored in a covered bottle at room temperature for several months without decomposition; the reagents can be weighed out in the air, and used directly for *N*-benzoylation.

We first investigated the benzoylating reactivity of various *N,N*-dibenzoylanilines **2** with respect to solvent (Table 2). All of the reagents evaluated reacted as a benzoylating reagent. The 2-unsubstituted dibenzoylaniline **2a** and 2-halogenated dibenzoylanilines **2c-e** were the most effective reagents. Every solvent evaluated (THF, CH_2Cl_2 , and *N,N*-dimethylformamide (DMF)) was suitable for the reaction. Primary, secondary, and *N*-methyl amines all gave good yields of the corresponding benzamides, although the reaction time required for comple-

Table 1. Preparation of Various *N,N*-Dibenzoylanilines **2a-e**



Entry	Starting 1 (<i>R</i>)	Recrystallized yield (%) of 2
1	H (1a)	86
2	Me (1b)	88
3	F (1c)	80
4	Cl (1d)	82
5	Br (1e)	79

r.t. = room temperature.

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tion depended on the bulkiness of amine. Even sterically hindered cumylamine (**6**) gave a moderate yield at 100°C in dioxane.¹⁰⁾

The substantial difference in reaction rates between hindered and less hindered amines prompted us to examine the selective benzoylation of amines. We chose to investigate the selectivity in the benzoylation of a 1:1 mixture of a hindered amine and a less hindered amine with the dibenzoylanilines **2a, c-e** (0.5 eq to total amines). The results are summarized in Table 3. 2-Chloro-*N,N*-dibenzoylaniline (**2d**) showed the highest selectivity (Table 3, entries 3, 4, 6). Comparison with Bz_2O , $BzCN$,⁴⁾ and Bz_2NOMe ,⁵⁾ the currently used reagents for *N*-benzoylation was also made (Table 3, entries 8-10). The selectivity was obviously worse, compared with the same reaction using 2-chloro-*N,N*-dibenzoylaniline (**2d**).

The generality of the above selective benzoylation by the dibenzoylaniline **2d** was tested with a variety of other substrates, with positive results, as indicated in Table 4. As can be seen, the less hindered benzoylated products were obtained in good yields.¹¹⁾

Table 2. *N*-Benzoylation of Various Amines Using **2a-e**

Entry	Amine	Reagent (R)	Solvent	Conditions	Product	Yield (%) ^a
1		H (2a)	THF	r.t., 2 h		95
2		Me (2b)	THF	30°C, 12 h		91
3		F	THF	r.t., 2 h		97
4		F	CH_2Cl_2	r.t., 2 h		96
5		F	DMF	r.t., 2 h		96
6		Cl (2d)	THF	r.t., 2 h		95
7		Cl	CH_2Cl_2	r.t., 2 h		97
8		Cl	DMF	r.t., 2 h		97
9		Br (2e)	THF	r.t., 2 h		97
10		F	THF	r.t., 2 h		97
11		Cl	THF	r.t., 1 h		95
12		Br	THF	r.t., 1 h		94
13		F	THF	r.t., 12 h		95
14		Cl	THF	r.t., 8 h		97
15		Br	THF	r.t., 10 h		93
16 ^{b)}		Cl	Dioxane	100°C, 72 h		70

a) Isolated yield. b) 2.0 eq of **2d** (2.0 eq) was used.

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Table 3. Competition Reaction

Entry	Benzoylating reagent	Solvent	Conditions		Yield (%) ^a	Selectivity ^b (7:9)
			Temp. (°C)	Time (h)		
1		THF	0, 24		89	11:1
2		THF	0, 24		—	11:1 ^c
3		THF	0, 24		91	>15:1
4		CH ₂ Cl ₂	0, 40		88	>15:1
5		DMF	0, 24		83	8:1
6		DMF	—30, 168		84	15:1
7		THF	0, 24		—	9:1 ^c
8	Bz ₂ O	11	THF	0, 1	92	5:1
9	BzCN	12	CH ₂ Cl ₂	0, 12	97	5:1
10	Bz ₂ NOMe	13	THF	0, 12	88	3:1

^a Isolated yield. ^b Determined by ¹H-NMR analysis after workup. ^c Determined by ¹H-NMR analysis of the crude product.

Table 4. Selective Benzoylation of Various Amines Using **2d** (1.05 eq) in THF at 0 °C

Entry	Substrate	Product	Time (h)	Yield (%) ^a
1			12	96
2 ^b			36	94
3			36	94

^a Isolated yield. ^b The reaction was run at -15 °C.

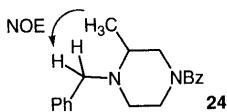
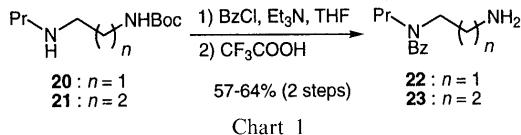


Fig. 1

In conclusion, 2-chloro-*N,N*-dibenzoylaniline (**2d**) is convenient to use, easy to handle, stable and effective in selective *N*-benzoylation. We believe that this novel benzoylating reagent can be widely used for the selective protection of various polyamino compounds.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on a JASCO FT/IR-230 diffraction grating infrared spectrophotometer. ¹H-NMR spectra were recorded with a JEOL GX-400 NMR spectrometer with tetramethylsilane as an internal standard. MS were obtained from a JEOL JMS-DX-303 instrument.

All starting amines were commercially available. In general, reactions were carried out in dry solvents under an argon atmosphere. CH₂Cl₂ was distilled under argon from CaH₂ before use. DMF was distilled under argon from CaH₂. THF was distilled under argon from sodium/benzophenone ketyl before use. All reagents were available from commercial sources and used without further purification.

2-Chloro-*N,N*-dibenzoylaniline (2d) To a stirred solution of 2-chloro-*N,N*-dibenzoylaniline (**1d**, 6.61 g, 28.5 mmol) in THF (80.0 ml) was gradually added BuLi (1.57 N in hexane, 19.7 ml, 31.0 mmol) at 0 °C, and the mixture was stirred for 20 min at 23 °C. To this solution was then added Bz₂O (7.00 g, 31.0 mmol) at 0 °C. The whole mixture was stirred at 23 °C for 1 h, quenched by the addition of sat. aq NH₄Cl, and extracted with ethyl acetate. The organic extracts were successively washed with H₂O, sat. aq NaHCO₃ and brine, dried (Na₂SO₄), and concentrated. The residual solid was recrystallized from ethyl acetate–hexane to give 2-chloro-*N,N*-dibenzoylaniline (**2d**) (7.81 g, 82%) as colorless prisms, mp 167–169 °C. IR (Nujol) cm⁻¹: 1703 (C=O), 1672 (C=O). ¹H-NMR (CDCl₃) δ: 7.10–7.55 (m, 10H, aromatic H), 7.75–7.80 (m, 4H, aromatic H). FAB-MS *m/z*: 338 (MH⁺ + 2), 336 (MH⁺). *Anal.* Calcd for C₂₀H₁₄CINO₂: C, 71.54; H, 4.20; N, 4.17. Found: C, 71.75; H, 4.06; N, 4.10.

Typical Procedure for an *N*-Benzoylation Corresponding to Table 3, Entry 1 To a stirred solution of amine **14** (76 μ l, 0.600 mmol) in THF (2.1 ml) was added 2-chloro-*N,N*-dibenzoylaniline (**2d**) (212 mg, 0.630 mmol) at 0 °C. The reaction mixture was stirred for 12 h at the same temperature and then concentrated. The residue was purified by silica gel column (ethyl acetate) to give *N*-benzoylamine **17** (121 mg, 96%) as a colorless oil. Chromatography was performed on Fuji Silysia NH-type silica gel chromatorex NHMD1020®.

N-Benzyl-*N'*-propylethylenediamine (17) A pale yellow oil. IR (neat) cm⁻¹: 3300 (NH), 1644 (C=O). ¹H-NMR (CDCl₃) δ: 0.90 (t, 3H, *J*=7.3 Hz, CH₂CH₂CH₃), 1.48 (tq, 2H, *J*=7.3, 7.3 Hz, CH₂CH₂CH₃), 1.57 (br s, 1H, NH), 2.58 (t, 2H, *J*=7.3 Hz, CH₂CH₂CH₃), 2.83 (t, 2H, *J*=5.9 Hz, NHCH₂CH₂NHCO), 3.49 (d, 1H, *J*=5.9 Hz, one of NHCH₂CH₂NHCO), 3.52 (d, 1H, *J*=5.9 Hz, one of NHCH₂CH₂NHCO), 6.98 (br s, 1H, NHCO), 7.36–7.49 (m, 3H, aromatic H), 7.76–7.80 (m, 2H, aromatic H). FAB-MS *m/z*: 207 (MH⁺). *Anal.* Calcd for C₁₂H₁₈N₂O: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.55; H, 8.91; N, 13.37.

Physical data of the other benzamides are shown below.

N-Benzylbenzamide (7) Colorless prisms (ethyl acetate–hexane), mp 107–109 °C [lit.¹²] mp 105–106 °C. IR (Nujol) cm⁻¹: 3288 (NH), 1634 (C=O). ¹H-NMR (CDCl₃) δ: 4.65 (dd, 2H, *J*=5.7, 1.8 Hz, 2H, CH₂), 6.49 (br s, 1H, NH), 7.27–7.82 (m, 8H, aromatic H), 7.77–7.82 (m, 2H, aromatic H). FAB-MS *m/z*: 212 (MH⁺).

N-Benzyl-*N*-methylbenzamide (8) A colorless oil. IR (neat) cm⁻¹: 1633 (C=O). ¹H-NMR (CDCl₃) δ: 2.86 and 3.03 (s, 3H, NCH₃), 4.51 and 4.76 (s, 2H, CH₂), 7.10–7.49 (m, 10H, aromatic H). FAB-MS *m/z*: 226 (MH⁺). *Anal.* Calcd for C₁₅H₁₅NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.84; H, 6.84; N, 6.18.

N-(α -Phenylethyl)benzamide (9) Colorless needles (ethyl acetate–hexane), mp 127–128 °C [lit.¹³] mp 124 °C. IR (Nujol) cm⁻¹: 3356 (NH), 1633 (C=O). ¹H-NMR (CDCl₃) δ: 1.61 (d, 3H, *J*=7.0 Hz, CHCH₃), 5.34 (dt, 1H, *J*=7.0, 7.0 Hz, CHCH₃), 6.24–6.40 (br, 1H, NH), 7.24–7.51 (m, 8H, aromatic H), 7.74–7.79 (m, 2H, arom-H). FAB-MS *m/z*: 226 (MH⁺).

N-Cumylbenzamide (10) Colorless needles (ethyl acetate–hexane), mp 161–163 °C [lit.¹⁴] mp 156–158 °C. IR (Nujol) cm⁻¹: 3258 (NH), 1635 (C=O). ¹H-NMR (CDCl₃) δ: 1.83 (s, 3H \times 2, CH₃), 6.39 (br s, 1H, NH), 7.22–7.51 (m, 8H, aromatic H), 7.73–7.78 (m, 2H, aromatic H). FAB-MS *m/z*: 240 (MH⁺).

N-Benzoyl-*N'*-propyl-1,3-propanediamine (18) A pale yellow oil. IR (neat) cm⁻¹: 3457 (NH), 3291 (NH), 1644 (C=O). ¹H-NMR (CDCl₃) δ: 0.93 (t, 3H, *J*=7.3 Hz, CH₂CH₂CH₃), 1.55 (tq, 2H, *J*=7.3, 7.3 Hz, CH₂CH₂CH₃), 1.57 (br s, 1H, NH), 1.77 (tt, 2H, *J*=5.9, 5.9 Hz, NHCH₂CH₂NHCO), 2.60 (t, 2H, *J*=7.3 Hz, CH₂CH₂CH₃), 2.83 (t, 2H, *J*=5.9 Hz, NHCH₂CH₂CH₂NHCO), 3.57 (br d, 1H, *J*=5.9 Hz, one of NHCH₂CH₂CH₂NHCO), 3.59 (br d, 1H, *J*=5.9 Hz, one of NHCH₂CH₂CH₂NHCO), 3.59 (br d, 1H, *J*=5.9 Hz, one of NHCH₂CH₂CH₂NHCO).

$\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NHCO}$), 7.38—7.50 (m, 3H, aromatic H), 7.78—7.83 (m, 2H, aromatic H), 8.31 (br s, 1H, NHCO). FAB-MS m/z : 221 (MH^+). HRFAB-MS m/z : 221.1647 (Calcd for MH^+ , $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}$: 221.1654).

1-Benzoyl-3-methylpiperazine (19) A pale yellow oil. IR (neat) cm^{-1} : 3308 (NH), 1623 (C=O). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 100 °C) δ : 0.93 (d, 3H, $J=6.2$ Hz, CHCH_3), 2.09 (br s, 1H, NH), 2.49—2.70 (m, 4H, CHCH_3 and CH_2), 2.80—3.00 (m, 3H, CH_2), 7.29—7.43 (m, 5H, aromatic H). FAB-MS m/z : 205 (MH^+). HRFAB-MS m/z : 205.1338 (Calcd for MH^+ , $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}$: 205.1341).

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- The *N,N*-dibenzoylanilines **2** could not be prepared at all with Bz_2O or BzCl in pyridine at 100 °C. For our *N,N*-diacylation conditions with an acylating reagent in pyridine, see: reference 7.
- Preparation of 2-trifluoromethyl-*N,N*-dibenzoylaniline was unsuccessful under these conditions ($\text{BuLi-Bz}_2\text{O}$).
- Benzoylation of aniline gave *N*-phenylbenzamide in 78% yield at 100 °C in dioxane.
- The regiochemistry of **17** was determined by comparison of $^1\text{H-NMR}$ data with **22**, prepared from **20** as shown in Chart 1. That of **18** was determined in a similar manner. The regiochemistry of **19** was determined by a NOE experiment of **24**, obtained on treatment of **19** with benzyl bromide and NaH in THF. The key NOE is shown in Fig. 1.
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