Facile Synthesis of Amidines from Thioamides

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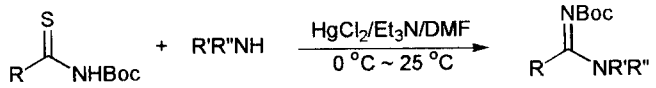
Received July 28, 1998

The amidine group is found occasionally in biologically active natural products, such as, antiviral amidinomycin,[1] antibiotic distamycin,[2] and noformicin[3] etc., and also has been employed as a skeletal component in the search for new pharmaceutical agents.[4] The amidine compounds are also used as structural unit for the synthesis of various heterocycles such as purines and pyrimidines.[5] A variety of methods for the preparation of amidines[6] have been reported in the literatures including direct addition of amines to nitriles with or without Lewis acids ($AlCl_3$, $ZnCl_2$ etc.)[7] at 150-200 °C or addition of amines to imino esters (Pinner's Method),[8,9] imino thioester, or imino chlorides.[10] Condensation of nitriles with amines catalyzed by lanthanide(III) triflate afforded *N,N'*-disubstituted or cyclic amidines but not monosubstituted amidines.[11] Examples of addition of amines to unactivated nitriles in the presence of cuprous chloride either with nitrile or refluxing alcohol as solvent were also reported.[12] But many of these methods suffer from harsh reaction conditions such as high temperature and/or strong acidic or basic conditions and are often incompatible with sensitive functional groups. Recently mild and efficient preparation of guanidines using *N*-(*t*-Boc)thioureas was reported.[13] It prompted us to apply similar procedure for the preparation of amidine from *N*-(*t*-Boc)thioamide. We report herein a mild and convenient method for preparation of *N*-*t*-Boc protected amidines from *N*-(*t*-Boc)thioamides (Scheme 1).

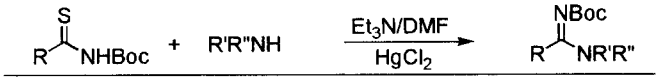
When *N*-(*t*-Boc)thioamides which were prepared from the thioamides and $(t\text{-Boc})_2O$ (NaH/THF, 0 °C) were allowed to react with various amines in the presence of $HgCl_2$ and Et_3N in DMF solvent at 0 °C or room temperature, *N*-(*t*-Boc)-*N'*-substituted amidines were obtained in excellent yields as shown in the Table 1, whereas reaction of unprotected thioacetamide with *p*-anisidine under the same conditions ($HgCl_2$, Et_3N, DMF, r.t., 24 hr.) did not afford amidine, but only unreacted p-anisidine was recovered quantitatively along with complete decomposition of thioacetamide (Scheme 2).

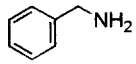
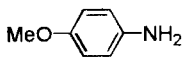
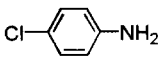
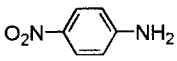
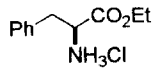
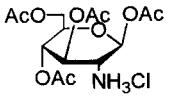
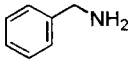
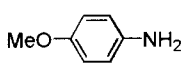
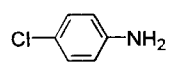
Reaction of *N*-(*t*-Boc)thioamides with amines seemed to be greatly affected both by the nucleophilicity and steric bulkiness of the amines and by the character of *N*-(*t*-Boc) thioamides. Amidination of *N*-(*t*-Boc)thioacetamide with simple aliphatic amines (entries 1, 2) proceeded faster than with aromatic amines (entries 4, 5). Reaction proceeded sluggishly in parallel with decreasing nucleophilicity of aniline by substitution with electron withdrawing group (entries 5, 6). Dramatic change was noticed by changing the substituent of aniline from *p*-MeO to *p*-NO_2 group. Only 20% of desired product was obtained from *p*-nitroaniline requiring prolonged reaction time (3 days) at room temperature. With sterically bulky *t*-butylamine (entry 3), amidination of *N*-(*t*-Boc)thioacetamide proceeded much slower rate taking 15 hrs at room temperature to complete the reaction. In contrast to *N*-(*t*-Boc)thioacetamide, amidination of *N*-(*t*-Boc)thiobenzamide was much slower (entries 10-13).

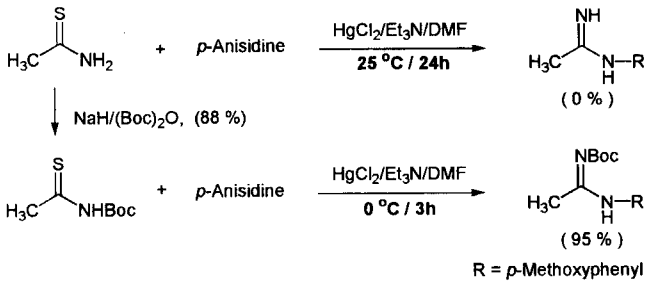


Scheme 1

Table 1. *N*-(*t*-Boc)amidines from *N*-(*t*-Boc)thioamides and amines



Entry	R	R'R"NH	Temp.(°C)	Time (hr)	Yield (%)
1	Me		0	1	98
2	Me		0	1	97
3	Me	*t*-Butylamine	25	15	97
4	Me		0	3	95
5	Me		25	3	95
6	Me		25	72	20
7	Me		25	4	90
8	Me		25	6	89
9	Ph		0	1	95
10	Ph		25	14	91
11	Ph		25	20	90
12	Ph		25	20	77
13	Ph		25	20	74



Scheme 2

However, reaction of highly nucleophilic benzylamine proceeded fast regardless of the type of thioamide (entries 1, 9).[14] Reaction of amine hydrochloride (entries 7-8) also proceeded smoothly with *N*-(*t*-Boc)thioamides to produce the corresponding *N*-(*t*-Boc)amidines. Deprotection of *t*-Boc group of *N*-(*t*-Boc)amidines was easily carried out using trifluoroacetic acid (CH_2Cl_2, r.t., 2hr.).[15] When we added *N*-(*t*-Boc) thioacetamide to DMF solution containing $HgCl_2$ and Et_3N before addition of the amine, we observed that starting *N*-(*t*-Boc)thioacetamide spot was instantaneously converted to a new single spot which disappeared smoothly upon addition of the amine to provide the corresponding *N*-(*t*-Boc)amidine spot. Although we suspect that the *in situ* generated intermediate might be the mercury complex species, efforts to isolate and identify intermediate of the reaction were fruitless due to its instability so far.

The typical experimental procedure is as follows. *N*-(*t*-Boc) thioacetamide: To the solution of thioacetamide (1.13 g, 15 mmol) in dry THF (150 mL) under nitrogen at 0 °C was added NaH (1.32 g, 33 mmol, 60% in mineral oil, hexane washed). After 30 minutes, cooling bath was removed and the reaction mixture was stirred at room temperature for additional 10 minutes. The reaction mixture was cooled again to 0 °C and neat di-*t*-butyl dicarbonate (3.60 g, 16.5 mmol) was added. After 30 minutes, cooling bath was removed and the reaction mixture was stirred for additional 2 hours at room temperature. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (20 mL) and poured into water (400 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash columm chromatography on silica gel eluting with hexane : ethyl acetate (5 : 1) to afford *N*-(*t*-Boc)thioacetamide as yellow crystalline solid (2.32 g, 88%). mp 54-55 °C. ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9H), 2.93 (s, 3H), 9.25 (s, 1H). MS m/e 175 (M^+), 119, 102, 58. *N*-(*t*-Boc)-*N'*-(*p*-chlorophenyl)acetamidine: To a solution of *N*-(*t*-Boc)thioacetamide (87.6 mg, 0.5 mmol), *p*-chloroaniline (63.8 mg, 0.5 mmol) and triethylamine (167 mg, 1.65 mmol) in dry DMF (3 mL) at 0 °C was added mercury (II) chloride (150 mg, 0.55 mmol) with stirring. After 5 minutes at 0 °C, cooling bath was removed and the reaction mixture was stirred for 3 hours at room temperature. The black reaction mixture was diluted with ethyl acetate (20 mL), and filtered through a pad of celite. The filtrate solution was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting hexane : ethyl acetate (4 : 1) to afford *N*-(*t*-Boc)-*N'*-(*p*-chlorophenyl) acetamidine (128 mg, 95%) as white solid. mp 119-120 °C. ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.18 (s, 3H), 7.2-7.4 (m, 4H). MS m/e 271 (M^++2), 269 (M^+), 170, 169, 168, 167, 156, 154, 129, 127, 58.

In summary, we have developed mild and efficient method for the preparation of amidines by combining amines with *N*-(*t*-Boc)thioamides which were prepared from thioamides and $(t\text{-Boc})_2O$.

Acknowledgment. We thank the Ministry of Science and Technology of Korea for financial support.

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