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Study on the reactions of azo compounds with acyl halides mediated by Sm/$TiCl_4$*

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Abstract: Amides can be obtained in good to excellent yield by Sm/$TiCl_4$ mediated reductive cleavage of N=N bond in azo compounds and successive acylation in one pot. It offers an alternative method for the synthesis of amides from very simple starting materials directly.

Key words: Azo compounds, Reduction, Amides, Sm/$TiCl_4$
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INTRODUCTION

Amides are important commercial and biological compounds. Because amides constitute the backbone of protein molecules, their chemistry is of extreme importance. The penicillin and cephalosporin antibiotics are among the best-known products of the pharmaceutical industry. For this reason, the development of new and simple methods for the synthesis of the peptide bond always constitute an important addition to the field of natural products synthesis. Several general methods are available for the preparation of amides, such as starting amines with acyl chlorides, acid anhydrides, esters, carboxylic acids, and carboxylic salts. All of these methods involve nucleophilic addition-elimination reaction by ammonia or an amine at an acyl carbon. Amides can also be made from Beckmann rearrangement of ketoximes (Donaruma and Heldt, 1960; Gawley, 1988) and conversion of thioamides into amides (Movassagh *et al*., 2002).

Samarium diiodide (SmI_2) has played an ever-increasing role in organic synthesis since its introduction by Kagan's group (Girard *et al*., 1980; Krief and Laval 1999; Molander, 1998; Molander and Harris, 1996; 1998). Though SmI_2 is a useful reductive reagent, its application in organic synthesis is limited in some extent. For example, Sm^{2+} is very sensitive to air and only gives one electron in the reaction, which restricts its application in large scale.

However, metallic samarium is stable in air, and its strong reducing power (Sm^{3+}/Sm=−2.41 V), is comparable to that of magnesium (Mg^{2+}/Mg=−2.37 V), and superior to that of zinc (Zn^{2+}/Zn=−0.71 V). Therefore, the direct use of metallic samarium as a reducing agent in organic transformations has attracted considerable attention in recent years (Banik, 2002). In most cases, reactions promoted by samarium are usually carried out in THF, and metallic samarium has to be activated or pretreated by various methods so as to ensure smooth reactions.

On the other hand, azo compounds serve as suitable models because they are easy to handle and the products are readily identified. Azo compounds

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can also be obtained by reductive cleavage of an azo linkage of either symmetric or unsymmetric azoarenes which permits two functional groups to be introduced into the aromatic nuclei and this is one of the easiest methods for the preparation of substituted aminoarenes. As azoarenes are easily accessible, it would be desirable to develop an easier and simpler method for the reduction of the N=N bond without affecting the substituents. Previous reports on the reductive cleavage of azo compounds into aminoarenes have been reviewed (Gilchrist, 1991). Souppe *et al*.(1983) reported that azobenzene can be reduced by SmI_2 to give moderate yields of amines if methanol is present. Our previous work (Li and Zhang, 2000) reported the synthesis of amidines from azo compounds and nitriles promoted by SmI_2 in THF.

To the best of our knowledge, there data on the synthesis of amides from azo compounds by Sm/$TiCl_4$ system in one pot without isolating the intermediate are not available. In continuing our research in this area (Chen and Zhang, 2004; Zhang *et al*., 2004), we wish to present Sm/$TiCl_4$ mediated reductive cleavage of N=N bond in azo compounds to form a reactive intermediate aniline anion which was immediately acylated to yield amides (Fig.1). This reaction can be completed in one pot with the reaction being mild and neutral.

Our first attempt was carried out by using azobenzene **1e** and benzoyl chloride **2e** as model substrates. Table 1 shows that when **1e** was treated with 2.2 equiv. Sm/$TiCl_4$ in THF solution at room temperature, it took two hours to finish the reaction after the addition of **2e**, with the yield of **3e** being 37%. On the other hand, when the temperature was increased to 65 °C, it took 10 min to yield 87% of **3e**. Generally, according to the results of the experiment, the ideal temperature for this reaction was 65 °C. Interestingly, the same products **3e** were obtained at a little lower yield while using benzoic anhydride **2d** instead of **2e**. It was ascribed to the higher reactivity of benzoyl chloride than that of the benzoic anhydride.

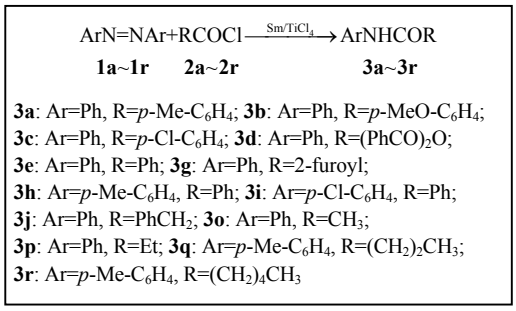

Fig.1 Synthesis of amides from azo compounds by Sm/$TiCl_4$ system

Table 1 Synthesis of amides from azobenzene by Sm/$TiCl_4$

Entry	Ar	R	Temperature (°C)	Time (min)	Yield of 3[a] (%)
a	Ph	*p*-Me-C_6H_4	65	15	83 (**3a**)
b	Ph	*p*-MeO-C_6H_4	65	10	85 (**3b**)
c	Ph	*p*-Cl-C_6H_4	65	15	87 (**3c**)
d[b]	Ph	$(PhCO)_2O$	65	15	81 (**3e**)
e	Ph	Ph	65	10	87 (**3e**)
f	Ph	Ph	rt	120	37 (**3e**)
g	Ph	2-furoyl	65	10	85 (**3g**)
h	*p*-Me-C_6H_4	Ph	65	8	89 (**3h**)
i	*p*-Cl-C_6H_4	Ph	65	8	84 (**3i**)
j	Ph	$PhCH_2$	65	6	95 (**3j**)
k[c]	Ph	Phthalic anhydride	65	15	–[d]
l	Ph	2-COCl-C_6H_4	65	15	–[d]
m	Ph	2-Me-C_6H_4	65	10	–[d]
n	Ph	2,4-diCl-C_6H_3	65	10	–[d]
o	Ph	CH_3	65	5	74 (**3o**)
p	Ph	CH_2CH_3	65	5	82 (**3p**)
q	*p*-MeC_6H_4	$(CH_2)_2CH_3$	rt	12	89 (**3q**)
r	*p*-MeC_6H_4	$(CH_2)_4CH_3$	rt	15	84 (**3r**)

[a]Isolated yields based on azobenzenes. All products were characterized by IR, ^{1}H NMR and MS; [b]Using benzoic anhydride instead of benzoyl chloride; [c]Using phthalic anhydride instead of benzoyl chloride; [d]The resulting residue was a complicated mixture which defied further separation and identification

Accordingly, with a view to further investigate the reaction, a series of aromatic acyl chlorides **2** were subjected to the acylation of **1** under the above optimized reaction conditions. To our delight, most of the reactions yielded smoothly under the same conditions and a variety of amides were obtained in good to excellent yields by Sm/$TiCl_4$ system, as shown in Table 1.

However, the reaction is strongly influenced by the substituent on the *o*-position of the benzoyl chlorides. When such substrates were used (Entry **2k**, **2l**, **2m**, **2n**), the resulting residue was a complicated mixture that defied further separation and identification. Perhaps it was the steric block that hindered the acylation.

In conclusion, amides can be obtained in good to excellent yield by Sm/$TiCl_4$ mediated reductive cleavage of N=N bond in azobenzene and successive acylation in one pot. It offers an efficient alternative method for the synthesis of amides directly from very simple starting materials.

EXPERIMENT DETAILS AND RESULTS

Melting points were uncorrected. Infrared spectra were recorded on a Bruker Vector-22 spectrometer in KBr. ^{1}H NMR spectra were measured in DMSO-d_6 or $DCCl_3$ solutions on a Bruker AC-400 Spectrometer with TMS as the internal standard. Mass spectra were recorded on a HP 5989B MS spectrometer (70 eV). THF was freshly distilled from sodium-benzophenone before use. Metallic samarium and other reagents were purchased from commercial sources and were used without further purification.

General procedure for the synthesis of amides from azo compounds by Sm/$TiCl_4$

Under nitrogen atmosphere, 1 mmol of azo compound (**1**) dissolved in dry THF (1 ml) was added to the solution of 2.2 mmol Sm/$TiCl_4$ in THF (10 ml). The deep blue color of the solution changed to brown gradually. After 4 mmol of aromatic acid anhydride (**2**) was added to the mixture, the color of the solution changed slowly to yellow. When the reaction monitored by TLC was completed, the reaction mixture was quenched with 0.1 mol/L hydrochloric acid (2 ml) and extracted with ether (20 ml×3). The organic phase was successively washed with water (20 ml), brine (15 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give crude products, which were purified by preparative TLC using ethyl acetate and cyclohexane (1:3) as eluent.

Compound **3a**: m.p. 145~147 °C. ^{1}H NMR ($CDCl_3$) 2.42 (s, 3H), 7.21~7.47 (m, 10H). IR (KBr) 3445 cm^{-1}, 1655 cm^{-1}. MS (*m*/*z*) 211 (M^+), 107, 93, 51.

Compound **3b**: m.p. 170~172 °C. ^{1}H NMR ($CDCl_3$) 3.85 (s, 3H), 6.76~7.54 (m, 10H). IR (KBr) 3395 cm^{-1}, 1655 cm^{-1}. MS (*m*/*z*) 227 (M^+), 135 (100), 107, 92, 77, 51.

Compound **3c**: m.p. 191~193 °C. ^{1}H NMR ($CDCl_3$) 7.21~8.05 (m, 9H), 7.76 (s, 1H). IR (KBr) 3389 cm^{-1}, 1655 cm^{-1}. MS (*m*/*z*) 231 (M^+), 139 (100), 93, 77, 51.

Compound **3e**: m.p. 161~163 °C. ^{1}H NMR (DMSO-d_6) 7.12 (t, 1H, *J*=7.6 Hz), 7.35 (m, 2H), 7.55 (m, 3H), 7.77 (d, 2H, *J*=7.2 Hz), 7.94 (m, 2H), 10.24 (s, 1H). IR (KBr) 3445 cm^{-1}, 1650 cm^{-1}. MS (*m*/*z*) 197 (M^+), 105, 93, 77, 65, 51.

Compound **3g**: m.p. 121~123 °C. ^{1}H NMR ($CDCl_3$) 5.63 (s, 1H, dispeared in D_2O), 6.86 (m, 3H), 7.20 (m, 5H); IR (KBr) 3316 cm^{-1}, 1660 cm^{-1}. MS (*m*/*z*) 187 (M^+), 92, 81, 77, 65.

Compound **3h**: m.p. 158~159 °C. ^{1}H NMR ($CDCl_3$) 2.35 (s, 3H), 7.10 (d, 2H, *J*=7.6 Hz), 7.51 (m, 5H), 7.74 (bs, 1H), 7.83 (d, 2H, *J*=7.6 Hz). IR (KBr) 3330 cm^{-1}, 1660 cm^{-1}. MS (*m*/*z*) 211 (M^+), 105 (100), 77, 51.

Compound **3i**: m.p. 192~194 °C. ^{1}H NMR (DMSO-d_6) 7.31~8.05 (m, 9H), 9.32 (s, 1H). IR (KBr) 3329 cm^{-1}, 1655 cm^{-1}. MS (*m*/*z*) 231 (M^+), 121, 105 (100), 77, 51.

Compound **3j**: m.p. 116~118 °C. ^{1}H NMR (DMSO-d_6) 3.63 (s, 2H), 7.05~7.61 (m, 10H), 10.14 (s, 1H). IR (KBr) 3295 cm^{-1}, 1664 cm^{-1}. MS (*m*/*z*) 211 (M^+), 93 (100), 77, 51.

Compound **3o**: m.p. 113~115 °C. ^{1}H NMR (DMSO-d_6) 2.03 (s, 3H), 7.02~7.56 (m, 5H), 9.90 (s, 1H). IR (KBr) 3295 cm^{-1}, 1665 cm^{-1}. MS (*m*/*z*) 135 (M^+), 93 (100), 43.

Compound **3p**: m.p. 106~108 °C. ^{1}H NMR (DMSO-d_6) 1.08 (t, 3H, *J*=6.0 Hz), 2.32 (q, 2H, *J*=6.0 Hz), 7.01~7.60 (m, 5H), 9.82 (s, 1H). IR (KBr) 3305 cm^{-1}, 1665 cm^{-1}. MS (*m*/*z*) 149 (M^+), 93 (100), 57.

Compound **3q**: m.p. 74~76 °C. ^{1}H NMR (DMSO-d_6) 0.90 (t, 3H, J=7.6 Hz), 1.60 (m, 2H), 2.23 (s, 3H), 2.26 (t, 2H, J=7.2 Hz), 7.08~7.47 (m, 4H), 9.73 (s, 1H). IR (KBr) 3297 cm^{-1}, 1665 cm^{-1}. MS (m/z) 177 (M^+), 107 (100), 91, 77, 43.

Compound **3r**: m.p. 74~75 °C. ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H, J=7.6 Hz), 1.28 (m, 4H), 1.57 (m, 2H), 2.23 (s, 3H), 2.28 (t, 2H, J=7.6 Hz), 7.08~7.47 (m, 4H), 9.73 (s, 1H). IR (KBr) 3305 cm^{-1}, 1669 cm^{-1}. MS (m/z) 205 (M^+), 107 (100), 91, 77, 43.

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