One Pot Preparation of Amides from Azo Compounds by Sm/$TiCl_4$

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Azo compounds were conveniently reduced by a system consisting of Sm/$TiCl_4$ to produce aniline anions. This anion species reacted smoothly with aliphatic acyl chlorides or acid anhydrides to afford corresponding amides under mild and neutral conditions.

Keywords: Amides; Azo compound; Sm/$TiCl_4$; Reduction.

INTRODUCTION

Amides are important commercial and biological compounds. Because amides constitute the backbone of protein molecules, their chemistry is of extreme importance. The peniciline and cephalosporin antibiotics are among the best-known products of the pharmaceutical industry.[1] 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,[1] 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[2] of ketoximes and conversion of thioamides into amides.[3]

Samarium diiodide (SmI_2) has played an ever-increasing role in organic synthesis since its introduction by Kagan's group.[4] Though SmI_2 is a useful reductive reagent, its application in organic synthesis is limited to some extent. For example, Sm^{2+} only gives one electron in the reaction, which seriously restricts its application in large scale use.

However, metallic samarium is stable in air, and its strong reducing power (Sm^{3+}/Sm = -2.41 V), is comparable with 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.[5]

On the other hand, azo compounds serve as suitable models because they are easy to handle and the products are readily identified. Azo compounds can also be reductive cleavages of an azo linkage of either symmetric or unsymmetric azoarenes that 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 valuable 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 azoarenes to aminoarenes have been reviewed.[6a] The reduction of azo compounds is usually achieved with Pd/Cyclohexene,[6b] multimetallic cluster (Mo_{x-1}, W_{x-1})[6c] center, KBH_4/Cu_2Cl_2,[6d] Pd/C,[6e] $NaBH_4/Cp_2TiBH_4$,[6f] PdMCM-41[6g] and Al/NH_2NH_2[6h] to form anilines. Kagan[6i] reported that azobenzene can be reduced by SmI_2 to give moderate yields of amines if methanol is present. In our previous work, Li[7] reported synthesis of amidines from azobenzene and nitriles promoted by SmI_2 in THF.

To the best of our knowledge, there is no data on synthesis of amides from azobenzene by Sm/$TiCl_4$ directly; herein, we wish to present the Sm/$TiCl_4$ mediated reductive cleavage of N=N bond in azobenzene and successive acylation to prepare amides. This reaction can be finished in one pot without separating the intermediate aniline, and the reaction conditions were mild and neutral.

RESULTS AND DISCUSSION

In order to optimize the reaction, various reactions in THF solvent using azobenzene (**1b)** and propanoic anhydride (**2b**) as model substrates were studied (Scheme I). Interest-

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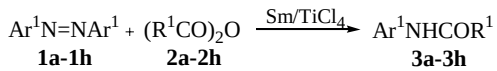
ingly, the best proportion of the substrate employed **1**:**2** = 1:4. Just as Table 1 shows when **1b**:**2b** = 1:1, the yield of N-phenyl propionamide (**3b)** was only 42%, while when **1b**:**2b** = 1:4, the yield of **3b** was 82%. Notably, temperature influences the reaction remarkably. Hardly any **3b** was observed in such reaction systems after 5 min at room temperature, and on the other hand, **3b** noticeably increased when the reaction temperature exceeded 65 °C. Generally, according to the results of the experiment, the ideal temperature for this reaction was 65 °C. And Table 1 also indicated that when the reaction finished in 5 min, the yield of **3b** didn't improve greatly when prolonging the reaction time.

Scheme I



1a-1h **2a-2h** **3a-3h**

3a: Ar^1= Ph-, R^1= CH_3-; **3b**: Ar^1= Ph-, R^1= CH_3CH_2-;
3c: Ar^1= Ph-, R^1= $CH_3(CH_2)_2$-; **3d**: Ar^1= Ph-, R^1= $CH_3(CH_2)_4$-;
3e: Ar^1= *p*-MeC_6H_4-, R^1= CH_3-;
3f: Ar^1= *p*-MeC_6H_4-, R^1= CH_3CH_2-;
3g: Ar^1= *p*-MeC_6H_4-, R^1= $CH_3(CH_2)_2$-;
3h: Ar^1= *p*-MeC_6H_4-, R^1= $CH_3(CH_2)_4$-.

To explore the generality of this reaction, a series of aliphatic acyl chlorides and acid anhydrides were subjected to the acylation with **1** and **2**; as anticipated, a variety of amides were obtained in good to excellent yields in the $Sm/TiCl_4$ system, as shown in Table 2 and Table 3. Both acyl chlorides and acid anhydrides could react smoothly to yield corresponding amides. When acetyl chloride (**4a)** was used instead of acetic anhydride (**2a**) in the reaction, the same product N-phenylacetamide (**3a)** was obtained at a higher yield. This is attributed to the more reactive substrate of acyl chloride than that of the acid anhydride. And all products were characterized by IR, ^{1}H NMR and MS.

In conclusion, amides can be obtained from moderate to good yield by $Sm/TiCl_4$ mediated reductive cleavage of the N=N bond in azo and successive acylation by acyl chloride or acid anhydride. This one-pot method offers a facile, efficient and novel route for the synthesis of amides.

Table 1. Reactions of **1b** and **2b** in different conditions

Entry	Molar ratio of the reactants	Temp. (°C)	Time (min)	Yield[a] of **3b** (%)
a	**1b**:**2b** = 1:1	65	5	42
b	**1b**:**2b** = 1:2	65	5	60
c	**1b**:**2b** = 1:3	65	5	73
d	**1b**:**2b** = 1:4	65	5	82
e	**1b**:**2b** = 1:4	40	10	20
f	**1b**:**2b** = 1:4	rt	10	trace
g	**1b**:**2b** = 1:4	65	15	85

[a] Isolated yields based on azobenzene.

Table 2. Synthesis of amides from acid anhydrides

Entry	Ar^1	R^1	Temp. (°C)	Time (min)	Yield[a] **3** (%)
a	Ph	CH_3	65	5	74(**3a**)
b	Ph	CH_2CH_3	65	5	82(**3b**)
c	Ph	$(CH_2)_2CH_3$	65	5	81(**3c**)
d	Ph	$(CH_2)_4CH_3$	65	5	83(**3d**)
e	*p*-MeC_6H_4	CH_3	rt	8	75(**3e**)
f	*p*-MeC_6H_4	CH_2CH_3	rt	8	85(**3f**)
g	*p*-MeC_6H_4	$(CH_2)_2CH_3$	rt	8	84(**3g**)
h	*p*-MeC_6H_4	$(CH_2)_4CH_3$	rt	10	81(**3h**)

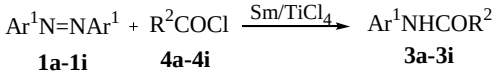
[a] Isolated yields based on azobenzene.

Table 3. Synthesis of amides from acyl chlorides

Entry	Ar^1	R^2	Temp. (°C)	Time (min)	Yield[a] **3** (%)
a	Ph	CH_3	65	6	76(**3a**)
b	Ph	CH_2CH_3	65	7	85(**3b**)
c	Ph	$(CH_2)_2CH_3$	65	6	83(**3c**)
d	Ph	$(CH_2)_4CH_3$	65	6	80(**3d**)
e	*p*-MeC_6H_4	CH_3	rt	10	79(**3e**)
f	*p*-MeC_6H_4	CH_2CH_3	rt	10	87(**3f**)
g	*p*-MeC_6H_4	$(CH_2)_2CH_3$	rt	12	89(**3g**)
h	*p*-MeC_6H_4	$(CH_2)_4CH_3$	rt	15	84(**3h**)
i	Ph	CH_2Ph	65	6	95(**3i**)

[a] Isolated yields based on azobenzene.

Scheme II



1a-1i **4a-4i** **3a-3i**

3a: Ar^1= Ph-, R^1= CH_3-; **3b**: Ar^1= Ph-, R^1= CH_3CH_2-;
3c: Ar^1= Ph-, R^1= $CH_3(CH_2)_2$-; **3d**: Ar^1= Ph-, R^1= $CH_3(CH_2)_4$-;
3e: Ar^1= *p*-MeC_6H_4-, R^1= CH_3-;
3f: Ar^1= *p*-MeC_6H_4-, R^1= CH_3CH_2-;
3g: Ar^1= *p*-MeC_6H_4-, R^1= $CH_3(CH_2)_2$-;
3h: Ar^1= *p*-MeC_6H_4-, R^1= $CH_3(CH_2)_4$-;
3i: Ar^1= Ph-, R^1= $PhCH_2$-.

EXPERIMENTAL SECTION

Melting points were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr. ^{1}H NMR spectra was measured in d_6-DMSO 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 distilled from sodium-benzophenone immediately prior to use. Metallic samarium and other reagents were purchased from commercial sources and were used without further purification.

General Procedure

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 immediately. After 4 mmol acid anhydrides (**2**) were added to the mixture, the color of the solution changed to yellow gradually. When the reaction was completed (the reaction was monitored by TLC), the reaction mixture was quenched with 0.1 M hydrochloric acid (2 mL) and extracted with ether (3 × 20 mL). 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.

DATA OF THE PRODUCTS

$PhNHCOCH_3$ (3a)

mp 113-115 °C (Lit.[8] 115-116 °C); IR (KBr) υ: 3295, 1665 cm^{-1}; ^{1}H NMR δ: 2.03 (s, 3H), 7.02-7.56 (m, 5H), 9.90 (s, 1H); MS (*m/z*): 135 (M^+), 93 (100), 43.

$PHNHCOCH_2CH_3$ (3b)

mp 106-108 °C (Lit.[9] 105-106 °C); IR (KBr) υ: 3305, 1665 cm^{-1}; ^{1}H NMR δ: 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); MS (*m/z*): 149 (M^+), 93 (100), 57.

$PhNHCOCH_2CH_2CH_3$ (3c)

mp 91-93 °C (Lit.[10] 91-92 °C); IR (KBr) υ: 3297, 1660 cm^{-1}; ^{1}H NMR δ: 0.91 (t, 3H, *J* = 7.6 Hz), 1.62 (m, 2H), 2.28 (t, 2H, *J* = 7.6 Hz), 7.03-7.60 (m, 5H), 8.57 (s, 1H); MS (*m/z*): 163 (M^+), 93 (100), 43.

$PhNHCO(CH_2)_4CH_3$ (3d)

mp 97-98 °C (Lit.[11] 97-98 °C); IR (KBr) υ: 3295, 1675 cm^{-1}; ^{1}H NMR δ: 0.90 (3H, t, *J* = 7.2 Hz), 1.30-1.71 (6H, m), 2.33 (2H, t, *J* = 7.2 Hz), 7.03-7.65 (5H, m), 9.57 (1H, br, s, NH); MS (*m/z*): 191 (M^+), 93 (100), 77, 43.

***p*-$MeC_6H_4NHCOCH_3$ (3e)**

mp 148-150 °C (Lit.[12] 150 °C); IR (KBr) υ: 3250, 1655 cm^{-1}; ^{1}H NMR δ: 2.13 (s, 3H), 2.31 (s, 3H), 7.03-7.45 (m, 4H), 9.70 (s, 1H); MS (*m/z*): 149 (M^+), 107 (100), 91, 77.

***p*-$MeC_6H_4NHCOCH_2CH_3$ (3f)**

mp 124-126 °C (Lit.[13] 121-123 °C); IR (KBr) υ: 3296, 1675 cm^{-1}; ^{1}H NMR δ: 1.07 (t, 3H, *J* = 7.2 Hz), 2.24 (s, 3H), 2.30 (q, 2H), 7.07-7.46 (m, 4H), 9.73 (s, 1H); MS (*m/z*): 163 (M^+), 107 (100), 91, 77, 57.

***p*-$MeC_6H_4NHCO(CH_2)_2CH_3$ (3g)**

mp 74-76 °C (Lit.[14] 74.6-74.8 °C); IR (KBr) υ: 3297, 1665 cm^{-1}; ^{1}H NMR δ: 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); MS (*m/z*): 177 (M^+), 107 (100), 91, 77, 43.

***p*-$MeC_6H_4NHCO(CH_2)_4CH_3$ (3h)**

mp 74-75 °C (Lit.[15] 74-75 °C); IR (KBr) υ: 3305, 1669 cm^{-1}; ^{1}H NMR δ: 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); MS (*m/z*): 205 (M^+), 107 (100), 91, 77, 43.

$PhNHCOCH_2Ph$ (3i)

mp 116-118 °C (Lit.[16] 118-119 °C); IR (KBr) υ: 3295, 1664 cm^{-1}; ^{1}H NMR δ: 3.63 (s, 2H), 7.05-7.61 (m, 10H), 10.14 (s, 1H); MS (*m/z*): 211 (M^+), 93 (100), 77, 51.

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REFERENCES

1. Atkins, R. C.; Carey, F. A. *Organic Chemistry, A Brief Course*; McGraw-Hill: New York, **1997**, *362.*
2. (a) Donaruma, L .G.; Heldt, W. Z. *Org. React.* **1960**, *11*, 1. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 1.
3. Movassagh, B.; Meibodi, F.; Sobhani, S. *Indian J. Chem.* **2002**, *41B*, 1296.
4. (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc*. **1980**, *102*, 2693-2698. (b) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745-777. (c) Molander, G. A. *Acc. Chem. Res*. **1998**, *31*, 603-609. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321-3354. (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307-338.
5. (a) Reviews see: Banik, B. K. *Eur. J. Org. Chem.* **2002**, 2431-2444. (b) Li, X.; Zhang, S.; Wang, Y.; Zhang, Y. *J. Chin. Chem. Soc.* **2002**, *49*, 1111. (c) Li, X.; Zhang, S.; Zhang, X.; Wang, X. *J. Chin. Chem. Soc.* **2003**, *50*, 1043. (d) Li, X.; Zhang, S.; Zhang, Y. *J. Chin. Chem. Soc.* **2004**, *51*, 347.
6. (a) Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Pergamon Press: Oxford, **1991**, *8*, 381. (b) Ho, T. L.; Olah, G. A. *Synthesis* **1977**, 169. (c) Sobota, P.; Pluziński, T.; Rummel, S. *Tetrahedron* **1981**, *37*, 939. (d) He, Y.; Zhao, H.; Pan, X.; Wang, S. *Synth. Commun*. **1989**, *19*, 3047. (e) Alper, H.; Vasapollo, G. *Tetrahedron Lett.* **1992**, *33*, 7477. (f) Dosa, P.; Kronish, I.; McCallum, J.; Schivartz, J.; Barden, M. C. *J. Org. Chem*. **1996**, *61*, 4886. (g) Selvam, P.; Sonavane, S. V.; Mohapatra, S. K.; Jayaram, R. V. *Tetrahedron Lett.* **2004**, *45*, 3071. (h) Pasha, M. A.; Nanjundaswamy, H. M. *J. Chem. Res(s).* **2004**, 750. (i) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227.
7. Li, Z. F.; Zhang, Y. M. *Chin. Chem. Lett.* **2000**, 495.
8. *Dictionary of Organic Compounds.* 5th Ed. Chapman and Hall: New York, 1982.
9. Weast, R. C.; Graffelli, J. G. *Handbook of Data on Organic Compounds*; 2nd Ed.; 1989.
10. Cruess, W. V.; Alsberg, C. L. *J. Am. Chem. Soc.* **1934**, *56*, 2117.
11. Ueda, M.; Kawaharasaki, N.; Imai, Y. *Synthesis* **1982**, 933.
12. Sharghi, H.; Hosseini, M. *Synthesis* **2002**, 1057.
13. DE Feo, R. J.; Strickler, P. D. *J. Org. Chem.* **1963**, *28*, 2915.
14. Urry, W. H.; Nishihara, A.; Niu, H. Y. *J. Org. Chem.* **1967**, *32*, 347.
15. Underwood, H. W.; Gale, J. C. *J. Am. Chem. Soc.* **1934**, *56*, 117.
16. Shioiri, T.; Yokoyama, Y.; Kasai, Y.; Yamada, S. *Tetrahedron* **1976**, *32*, 2211.