$Rh_2(OAc)_4$-Mediated Diazo Decomposition of δ-(*N*-Tosyl)amino-β-keto-α-diazo Carbonyl Compounds: A Novel Approach to Pyrrole Derivatives

Guisheng Deng, Nan Jiang, Zhihua Ma, Jianbo Wang*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry, Peking University, Beijing 100871, P. R. China

Fax +86(10)62751708; E-mail: wangjb@pku.edu.cn

Received 20 August 2002

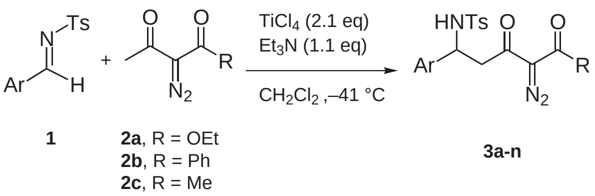
Abstract: (*N*-Tosyl)amino substituted β-keto diazo carbonyl compounds have been prepared by reaction of titanium enolate of β-ketodiazoester or -ketone with an activated *N*-tosylimine. $Rh_2(OAc)_4$-catalyzed reaction of the (*N*-tosyl)amino substituted α-diazocarbonyl compounds leads to the efficient formation of pyrrole derivatives.

Key words: pyrroles, diazo compounds, Ti(IV) enolate, nucleophilic additions, Rh(II) carbene

Pyrrole derivatives are important heterocycles widely used in material science and found in biologically important natural products.[1] In particular, the pyrroles bearing functional substituents have attracted great attention among the synthetic organic chemists, and various methodologies have been developed for synthesizing these compounds. Traditionally, pyrroles have been synthesized by the condensation of primary amine with 1,4-dicarbonyl compounds.[2,3] The obvious drawback of this approach, known as Paal–Knorr cyclocondensation, is the accessibility of suitable 1,4-dicarbonyl compounds. In this communication, we report a novel and highly efficient two-step reaction sequence leading to the functionalized pyrroles. This approach is based on nucleophilic condensation of an α-diazo-β-ketoester or an α-diazo-β-ketoketone with *N*-tosylimine followed by a Rh(II)-catalyzed diazo decomposition.[4]

Although the aldol condensation of α-diazo-β-ketoester has been developed by Calter et al.,[5] the corresponding condensation with imine is not reported. We expected the condensation of α-diazo-β-ketoester **2a**, and α-diazo-β-ketoketones **2b**, **2c** with *N*-sulfonylimines under the similar condition as for aldol reaction would occur to give α-diazocarbonyl compounds **3a**–**n**, which bear δ-(*N*-tosyl)amino group (Scheme 1). Thus, titanium(IV) enolate of α-diazo-β-ketoester is generated by treating the diazo ester with $TiCl_4$–Et_3N at –41 °C in CH_2Cl_2. However, direct reaction of *N*-tosylimine with the enolate did not yield the expected condensation product. To further increase the electrophilicity of C=N bond, *N*-tosylimine was activated by treating with another equivalent of $TiCl_4$ before reacting with the enolate. Under this condition, the expected condensation product was obtained in good yield.[6]

The generality of the procedure is shown by the reaction of a series of *N*-tosylimines with α-diazo-β-ketoesters and α-diazo-β-ketoketones (Table 1). The condensation with α-diazo-β-ketoesters gives moderate to good isolated yields in general, but the reaction with α-diazo-β-ketoketone **2c** gives only low yields (entries 12–14) due to the low reactivity of the corresponding enolate and the further aldol reaction of the products.



Scheme 1

Table 1 $TiCl_4$-Promoted Condensation of α-Diazo-β-Ketoesters **2** with *N*-Tosyl Imines **1**[a]

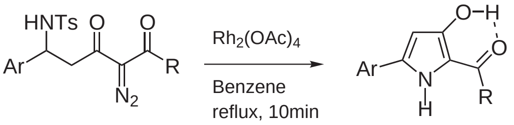
Entry	Diazo Substrate **2**	*N*-Tosyl imines **1** (Ar =)	Product	Yield (%)[b,c]
1	**2a**	C_6H_5	**3a**	62 (96)
2	**2a**	*o*-MeC_6H_4	**3b**	83 (98)
3	**2a**	*p*-FC_6H_4	**3c**	34 (94)
4	**2a**	*p*-ClC_6H_4	**3d**	47 (96)
5	**2a**	*m*-CNC_6H_4	**3e**	87 (97)
6	**2a**	*p*-$MeOC_6H_4$	**3f**	37 (92)
7	**2a**	(*E*)-CH=CHC_6H_5	**3g**	47 (94)
8	**2a**	2-Furyl	**3h**	74 (99)
9	**2a**	2-(5-Bromo)thienyl	**3i**	51 (93)
10	**2b**	2-Furyl	**3j**	58 (96)
11	**2b**	(*E*)-CH=CHC_6H_5	**3k**	70 (98)
12	**2c**	C_6H_5	**3l**	17 (37)
13	**2c**	*m*-BrC_6H_4	**3m**	17 (38)
14	**2c**	*p*-$MeOC_6H_4$	**3n**	13 (33)

[a] For general experimental procedure, see ref.[6]
[b] Isolated yield.
[c] Number in parenthesis refers to the conversion yield.

Synlett 2002, No. 11, Print: 29 10 2002.
Art Id.1437-2096,E;2002,0,11,1913,1915,ftx,en;U05602ST.pdf.

ISSN 0936-5214

With the δ-(*N*-tosyl)amino-β-oxo-α-diazo esters or ketones **3a**–**n** in hand, we proceeded to study the catalytic reaction with $Rh_2(OAc)_4$. The diazo decomposition of **3a** (Ar = C_6H_5) occurred very slowly in CH_2Cl_2 at room temperature in the presence of 1% mol of $Rh_2(OAc)_4$. However, when it was refluxed in benzene with $Rh_2(OAc)_4$, the diazo compound disappeared within 10 min, leading to clean formation of a new compound. Spectroscopic data of the isolated product confirmed its structure as 1-carboethoxy-2-hydroxy-5-phenylpyrrole **4a** (Ar = C_6H_5) (Scheme 2). The pyrrolidine derivative, which was expected to form through normal intramolecular N-H insertion of the Rh(II)-carbene intermediate,[7] was not observed in this reaction. Other diazo compounds all give similar results when reacted with catalytic $Rh_2(OAc)_4$ under the same condition to yield corresponding pyrrole derivatives in good yields (Table 2).[8] When the diazo compounds were decomposed with $Rh_2(O_2CCF_3)_4$ or $Cu(acac)_2$ in refluxing benzene, same pyrrole derivatives were obtained in identical yields.



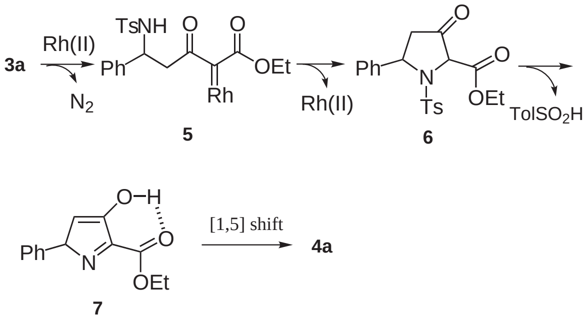
Scheme 2

Table 2 $Rh_2(OAc)_4$-Mediated Diazo Decomposition[a]

Entry	Diazo compound **3**	Product	Yield (%)[b]
1	**3a**	**4a** R = OEt, Ar = C_6H_5	75
2	**3b**	**4b** R = OEt, Ar = *o*-MeC_6H_4	73
3	**3e**	**4c** R = OEt, Ar = *m*-CNC_6H_4	64
4	**3g**	**4d** R = OEt, Ar = (*E*)-CH=CHC_6H_5	75
5	**3h**	**4e** R = OEt, Ar = 2-Furyl	91
6	**3i**	**4f** R = OEt, Ar = 2-(5-Bromo) thienyl	75
7	**3j**	**4g** R = C_6H_5, Ar = 2-Furyl	88
8	**3k**	**4h** R = C_6H_5, Ar = (*E*)-CH= CHC_6H_5	94
9	**3n**	**4i** R = Me, Ar = *p*-$MeOC_6H_4$	90

[a] For general experimental procedure and characterization data for **4a**–**i**, see ref.[8,]
[b] Isolated yield.

Although the chemistry of α-Diazocarbonyl compounds have been extensively investigated, the formation of pyrrole derivatives from α-diazocarbonyl compounds bearing a δ-(*N*-tosyl)amino group is unprecedented. A possible reaction pathway is outlined in Scheme 3. Intramolecular N-H insertion occurs to give **6**, from which $TolSO_2H$ is eliminated to give intermediate **7**.[9] Finally, [1,5]-shift of hydrogen gives the pyrrole derivative **4a**.



Scheme 3

In summary, the nucleophilic addition of titanium (IV) enolates of α-diazo-β-ketoester or α-diazo-β-ketoketone to *N*-tosylimines was successfully promoted by the activation of $TiCl_4$ to give δ-(*N*-tosyl)amino substituted β-keto diazo carbonyl compounds. The $Rh_2(OAc)_4$-catalyzed reaction of these diazo carbonyl compounds gives pyrrole derivatives in excellent yields.

Acknowledgement

The project is generously supported by Natural Science Foundation of China (Grant No. 29972002, 20172002), and by Trans-Century Training Programme Foundation for the Talents by Ministry of Education of China.

References

(1) *Comprehensive Heterocyclic Chemistry*, Vol. 2; Bird, C. W., Ed.; Pergamon Press: Oxford, **1996**.
(2) For recent examples of pyrrole syntheses based on Paal–Knorr reaction, see: (a) Hewton, C. E.; Kimber, M. C.; Taylor, D. K. *Tetrahedron Lett.* **2002**, *43*, 3199. (b) Takaya, H.; Kojima, S.; Murahashi, S.-I. *Org. Lett.* **2001**, *3*, 421. (c) Braun, R. U.; Zeitler, K.; Muller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (d) Surya Prakash Rao, H.; Jothilingam, S. *Tetrahedron Lett.* **2001**, *42*, 6595.
(3) For recent examples of pyrrole syntheses that are not based on Paal–Knorr reaction, see: (a) Chen, N.; Lu, Y.; Gadamasetti, K.; Hurt, C. R.; Norman, M. H.; Fotsch, C. *J. Org. Chem.* **2000**, *65*, 2603. (b) Katritzky, A. R.; Huang, T.-B.; Voronkov, M. V.; Wang, M.; Kolb, H. *J. Org. Chem.* **2000**, *65*, 8819. (c) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1339. (d) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (e) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887. (f) Lagu, B.; Pan, M.; Wachter, M. P. *Tetrahedron Lett.* **2001**, *42*, 6027.
(4) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley Interscience: New York, **1998**.
(5) (a) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tetrahedron Lett.* **1997**, *38*, 3837. (b) Calter, M. A.; Sugathapala, P. M. *Tetrahedron Lett.* **1998**, *39*, 8813. (c) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415.

(6) General procedure for the $TiCl_4$-promoted condensation of α-diazo-β-ketoester **1** with *N*-tosylimine: To a solution of **2a** (10.0 mmol) in anhydrous CH_2Cl_2 (20 mL) at –41 °C were added dropwise $TiCl_4$ (11.0 mmol) and Et_3N (11.0 mmol). After the resulting red-dark solution was stirred at –41 °C for 1 h, a solution of *N*-tosylimine (4 mmol) in anhydrous CH_2Cl_2 (4 mL) was added dropwise. The reaction mixture was stirred at –41 °C for 9 h and then was quenched with saturated aqueous NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), and then dried over Na_2SO_4. The product was purified by flash chromatography to yield **3a** (Ar = Ph) as white solid (1.03 g, 62%). Mp 140–142 °C; IR (KBr) 3223, 2152, 1748, 1625 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7 Hz, 3 H), 2.37 (s, 3 H), 3.19 (dd, *J* = 15.6, 5.4 Hz, 1 H), 3.36 (dd, *J* = 15.6, 8 Hz, 1 H), 4.28 (q, *J* = 7 Hz, 2 H), 4.76–4.86 (m, 1 H), 5.69 (d, *J* = 7.8 Hz, 1 H), 7.14–7.20 (m, 7 H), 7.58 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 21.4, 46.3, 54.5, 61.6, 76.8, 126.3, 127.0, 127.4, 128.4, 129.2, 137.4, 140.1, 143.0, 161.1, 189.8; MS *m/z* (FAB): 416 [$(M+H)^+$, 13], 388 (3), 344 (2), 261 (11), 245 (69), 219 (20), 181 (12), 171 (49), 139 (23), 115 (38), 91 (100), 77 (22), 59 (38), 41 (53). Anal. Calcd for $C_{20}H_{21}N_3O_5S$: C, 57.82; H, 5.09; N, 10.11. Found: C, 57.85; H, 5.09; N, 10.01.

(7) For examples of intramolecular N-H bond insertion, see: (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223. (b) Wang, J.; Hou, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2277.

(8) General procedure for the diazo decomposition of **3** with catalyst $Rh_2(OAc)_4$: A solution of **3a** (Ar = Ph, 1.0 mmol) in benzene (30 mL) containing $Rh_2(OAc)_4$ (0.01 mmol) was heated under reflux for 10 min. The solution was cooled to room temperature and was concentrated. Purification by flash chromatography provided **4a** (Ar = Ph, 75% yield) as white solid.

4a: Mp 138–140 °C; IR (KBr) 3453, 3304, 3278, 1692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.2 Hz, 3 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 6.16 (d, *J* = 3.2 Hz, 1 H), 7.25–7.79 (m, 5 H), 7.91 (br, s, 1 H), 8.76 (br, d, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 61.2, 95.9, 106.2, 124.9, 128.2, 128.6, 131.1, 136.0, 155.2, 162.0; MS *m/z* (EI) 231 (M^+, 91), 203 (3), 185 (100), 156 (18), 129 (12), 102 (72), 77 (14), 51 (6); Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.59; N, 5.91.

4b: Mp 91–93 °C; IR (KBr) 3489, 3310, 1696, 1677 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.2 Hz, 3 H), 2.43 (s, 3 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 5.98 (d, *J* = 2.6 Hz, 1 H), 7.23–7.37(m, 4 H), 7.76 (br, s, 1 H), 8.11 (br, s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 20.7, 60.0, 98.8, 105.5, 126.0, 128.3, 128.4, 130.9, 131.5, 135.7, 135.9, 153.7(br), 162.0(br); MS *m/z* (EI) 245 (M^+, 100), 222 (3), 199 (93), 193 (28), 171 (12), 144 (12), 134 (12), 123 (28), 116 (63), 95 (7), 91 (6), 77 (6), 57 (6), 43 (7). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.45; H, 6.18; N, 5.61.

4c: Mp 203 °C; IR (KBr) 3501, 3337, 2227, 1669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$/DMSO-d_6) δ 1.41 (t, *J* = 7.2 Hz, 3 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 6.17 (d, *J* = 2.8 Hz, 1 H), 7.44–7.56 (m, 2 H), 7.89–7.95 (m, 2 H), 8.15 (s, 1 H), 10.91 (br, s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$/DMSO-d_6) δ 14.1, 59.4, 95.7, 106.9, 112.0, 118.1, 128.0, 128.9, 129.9, 132.2, 132.5, 152.7, 161.4; MS *m/z* (EI) 256 (M^+, 14), 241 (2), 210 (20), 178 (5), 171 (43), 155 (57), 127 (14), 107 (22), 91 (100), 65 (39), 57 (31), 39 (18); Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.81; H, 4.59; N, 10.83.

4d: Mp 150–152 °C; IR (KBr) 3269, 1680, 1661 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$/DMSO-d_6) δ 1.37 (t, *J* = 7.2 Hz, 3 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 5.94 (d, *J* = 2.8 Hz, 1 H), 6.88 (d, *J* = 16.4 Hz, 1 H), 7.06 (d, *J* = 16.4 Hz, 1 H), 7.21–7.44 (m, 5 H), 7.91 (s, 1 H), 11.0 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$/DMSO-d_6) δ 14.0, 58.9, 94.8, 105.2, 117.6, 125.4, 126.9, 127.9, 128.3, 133.8, 136.0, 152.6, 161.1; MS *m/z* (EI) 257 (M^+, 100), 210 (88), 183 (11), 182 (6), 167 (8), 154 (28), 128 (46), 102 (5), 77 (6), 51 (5), 29 (5); Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.22; H, 6.08; N, 5.29.

4e: Mp 131–133 °C; IR (KBr) 3306, 1667, 1564 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.2 Hz, 3 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 6.06 (d, *J* = 2.6 Hz, 1 H), 6.45–6.47 (m, 1 H), 6.56 (d, *J* = 3.4 Hz, 1 H), 7.41–7.42 (m, 1 H), 7.92 (br s, 1 H), 8.59 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 60.1, 94.6, 105.4, 106.2, 111.7, 126.8, 142.0, 146.5, 154.4, 162.1; MS *m/z* (EI) 221 (M^+, 95), 193.3 (4), 175 (100), 147 (26), 139 (2), 119 (15), 92 (52), 91 (8), 63 (15), 39 (12); Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.65; H, 4.97; N, 6.13.

4f: Mp 129–130 °C; IR (KBr) 3502, 3289, 1677, 1574, 1539 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.2 Hz, 3 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 5.99 (d, *J* = 3Hz, 1 H), 6.93–7.26 (m, 2 H), 8.08 (br s, 1 H), 8.84 (br, s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 60.3, 96.6, 123.7, 127.9, 129.7, 130.7, 131.9, 139.0, 144.5, 160.9; MS *m/z* (EI) 317 (M^+, ^{80}Br, 74), 315 (M^+, ^{78}Br, 71), 271 (100), 242 (12), 215 (9), 188 (37), 162 (76), 155 (17), 133 (14), 108 (19), 91 (40), 82 (9), 63 (14), 45 (5); Anal. Calcd for $C_{11}H_{10}BrNO_3S$: C, 41.79; H, 3.19; N, 4.43. Found: C, 41.85; H, 3.26; N, 4.40.

4g: Mp 139–142 °C; IR (KBr) 3320, 1590, 1567 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.14 (d, *J* = 2.4 Hz, 1 H), 6.50 (dd, *J* = 3.5, 1.7 Hz, 1 H), 6.66 (d, *J* = 3.5 Hz, 1 H), 7.44 (d, *J* = 1.7 Hz, 1 H), 7.50–7.59 (m, 3 H), 7.77–7.82 (m, 2 H), 8.26 (br s, 1 H), 10.43 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 94.8, 108.2, 112.1, 116.0, 127.5, 129.0, 129.8, 131.6, 137.7, 142.7, 145.9, 159.3, 184.0; MS *m/z* (EI) 253 (M^+, 100), 236 (5), 224 (4), 196 (4), 176 (30), 147 (7), 120 (9), 105 (37), 92 (24), 91 (3), 77 (49), 65 (20), 51 (17), 39 (15); Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.98; H, 4.37; N, 5.46.

4h: Mp 159–161 °C; IR (KBr) 3322, 2261, 1626, 1592, 1550, 1503 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.10 (d, *J* = 2 Hz, 1 H), 6.79 (d, *J* = 16.5 Hz, 1 H), 7.00 (d, *J* = 16.5 Hz, 1 H), 7.28–7.54 (m, 8 H), 7.68–7.72 (m, 2 H), 8.41 (br s, 1 H), 10.40 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 96.3, 116.6, 117.3, 126.6, 127.5, 128.5, 128.8, 128.9, 131.6, 132.0, 135.9, 137.7, 138.0, 159.5, 183.8; MS *m/z* (EI) 289 (M^+, 100), 288 (27), 270 (10), 212 (13), 156 (6), 128 (23), 105 (49), 77 (31), 51 (7); Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.80; H, 5.21; N, 4.74.

4i: Mp 178–180 °C(decomposed); IR (KBr) 3272, 1614, 1585, 1534 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 3.85 (s, 3 H), 6.01 (d, *J* = 2.8 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 2 H), 9.47 (br s, 1 H), 10.59 (br, s, 1 H); MS *m/z* (EI) 231 (M^+, 100), 216 (93), 202 (9), 188 (5), 174 (8), 161 (15), 146 (4), 133 (18), 118 (7), 117 (8), 102 (3), 89 (12), 77 (4), 63 (6), 43 (13); Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.41; H, 5.71; N, 6.01.

(9) *p*-Toluenesufinic acid was further converted to thiosulfonic ester, which is isolated and characterized.