Tetrahedron Letters 49 (2008) 7161–7164

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile synthesis of fluorine-containing 1,10-phenanthrolines by the pyridine-ring formation reaction of *N*-propargyl-5,7-bis(trifluoroacetyl)-8-quinolylamine with amines: isolation of the intermediates 1,4-dihydro-1,10-phenanthrolin-4-ols

Dai Shibata [a], Etsuji Okada [b,*], Jérôme Molette [c], Maurice Médebielle [c]

[a] *Graduate School of Science and Technology, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan*
[b] *Department of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan*
[c] *Université de Lyon, Université Claude Bernard Lyon 1 (UCBL), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), Laboratoire de Synthèse de Biomolécules (LSB), UMR 5246 CNRS-UCBL-INSA Lyon-CPE Lyon, 43 Bd Novembre, Villeurbanne 69622, France*

ARTICLE INFO

Article history:
Received 2 September 2008
Revised 26 September 2008
Accepted 29 September 2008
Available online 7 October 2008

Keywords:
1,10-Phenanthrolines
Fluorine
Pyridine-ring formation
Propargylamines
8-Quinolylamines

ABSTRACT

Novel fluorine-containing 1,10-phenanthrolines having dialkyl-, alkyl, and arylaminomethyl substituents at the 3-position were easily synthesized in moderate yields by the pyridine-ring formation reaction of *N*-propargyl-5,7-bis(trifluoroacetyl)-8-quinolylamine with various amines. Unexpectedly, the reactive intermediates 1,4-dihydro-1,10-phenanthrolin-4-ols were isolated for the first time in the reactions with dialkylamines.

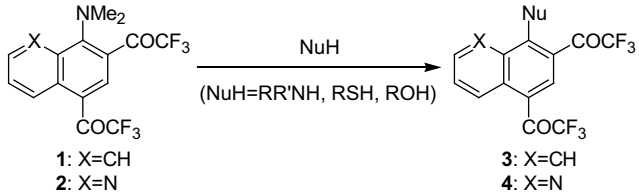
© 2008 Elsevier Ltd. All rights reserved.

In recent years, considerable attention has been paid to the development of new methodologies for the synthesis of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[1]

1,10-Phenanthroline and the related derivatives[2] have attracted much attention for their various biological activities, such as antibacterial,[3a,c] antifungal,[3a] and antitumor[3b,d] activities. They are also important heterocyclic systems because of being applicable to chelating ligands forming stable complexes with transition metals.[4] In particular, some of these complexes have been used as useful novel catalysts in phase-transfer[5] and asymmetric[6] reactions, and they are also potential DNA binding agents,[7,3d] which can be expected to be developed as novel probes of nucleic acid structure and function.

Previously, we had reported that *N*,*N*-dimethyl-2,4- bis(trifluoroacetyl)-1-naphthylamine **1**[8] and *N*,*N*-dimethyl- 5,7-bis(trifluoroacetyl)-8-quinolylamine **2**[9] react easily with various amines, thiols, and alcohols under mild conditions to afford the corresponding *N*–*N*, *N*–*S*, and *N*–*O* exchanged products **3** and **4** in excellent yields (Scheme 1). Moreover we succeeded in applying this type of aromatic nucleophilic substitution to the simple syntheses of various CF_3-containing heterocycles that are having a naphthalene[10] and a quinoline[11] skeletons.

In continuation of these studies, it was found that *N*-propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine **5**, prepared by *N*–*N* exchange reaction of **1** with propargylamine, undergoes novel pyridine-ring formation reaction with various nucleophiles to give the corresponding fluorine-containing benzo[*h*]quinolines **6** in excellent yields (Scheme 2).[12]



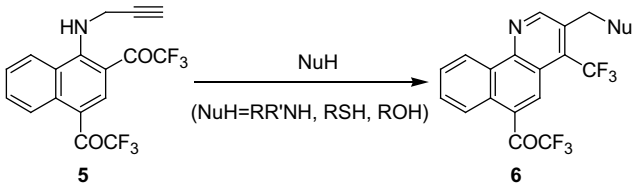
1: X=CH
2: X=N

3: X=CH
4: X=N

Scheme 1.

* Corresponding author. Tel./fax: +81 78 803 6194.
E-mail address: okaetsu@kobe-u.ac.jp (E. Okada).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.172



Scheme 2.

Herein, we report a facile synthetic method for novel fluorine-containing 1,10-phenanthrolines **9** by the pyridine-ring formation reaction of *N*-propargyl-5,7-bis(trifluoroacetyl)-8-quinolylamine **7** with amines and the isolation of the reactive intermediates 1,4-dihydro-1,10-phenanthrolin-4-ols, **8a**–**c**. To the best of our knowledge, this is the first example of the isolation of 1,4-dihydro-1,10-phenanthrolin-4-ols as the precursor of 1,10-phenanthrolines.

The requisite starting material **7** was quantitatively prepared by the aromatic nucleophilic *N*–*N* exchange reaction of **2** with propargylamine.[9]

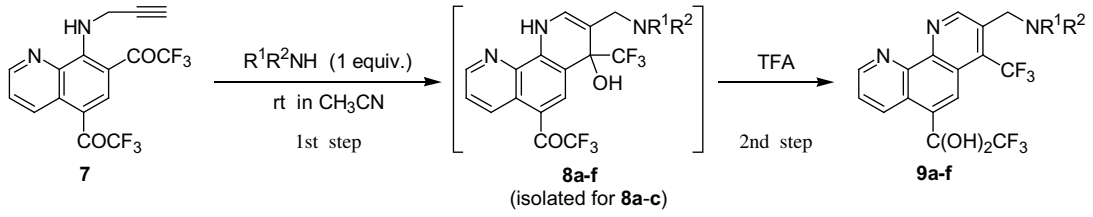
We first examined the reaction of **7** with secondary amines (Scheme 3), and the results are summarized in Table 1. The cyclization of **7** with dimethylamine proceeded rapidly at room temperature in CH_3CN to give the unexpected intermediate, 1,4-dihydro-1,10-phenanthrolin-4-ol **8a**, in an almost quantitative yield without dehydration (entry 1; in the first step).[13] Secondary amines such as diethylamine and piperidine also reacted cleanly to provide dihydrophenanthrolinols **8b** and **8c** quantitatively (entries 2 and 3). Treatment of dihydrophenanthrolinols **8a**–**c** with trifluoroacetic acid (TFA) caused dehydration to furnish the corresponding phenanthrolines **9a**–**c** in 60–63% yields (entries 1–3; in the second step).[14] The dehydration of piperidino derivative **8c** was carried out under mild conditions (with 1 equiv of TFA at room temperature in $CHCl_3$). However, forced reaction conditions (in refluxing TFA) were required for dimethyl- and diethylamino derivatives **8a** and **8b**. The reason is not clear at this stage. Interestingly, the 6-trifluoroacetyl group of prepared 1,10-phenanthrolines **9** was found to exist in hydrate form, and this phenomenon was not observed in the case of benzo[*h*]quinolines **6**.

In contrast, when the reaction with bulky primary amine such as *t*-butylamine was performed under mild conditions (at room temperature for 4 h), a mixture of dihydrophenanthrolinol **8d** and phenanthroline **9d** was obtained, and separation of the mixture was unsuccessful. Therefore, we performed the two-step reaction in a one-pot manner to obtain selectively the final target product **9d**. After stirring the solution of a mixture of **7** and *t*-butylamine in CH_3CN for 4 h at room temperature, TFA (5 equiv) was added to the reaction mixture, and then it was further stirred for 5 min at the same temperature to afford **9d** in 58% yield (entry 4). In a similar one-pot manner, aromatic primary amines, for example, *p*-anisidine and *p*-chloroaniline, reacted in the presence of triethylamine as a base to give the desired 1,10-phenanthrolines **9e** and **9f** in moderate yields (entries 5 and 6).[15] Unfortunately, the reactions with less bulky aliphatic primary amines such as methyl-, ethyl-, and *i*-propylamines furnished a complex mixture of the corresponding *N*–*N* exchanged 8-quinolylamine derivatives **4** (Nu: MeNH, EtNH and *i*-PrNH) and decomposed products.

A possible mechanistic pathway for the formation of 1,10-phenanthrolines is depicted in Scheme 4. Both the addition of amines to the terminal acetylenic carbon and the attack of carbonyl carbon onto the internal acetylenic carbon occur concertedly to give the cyclization product **8′** having *exo*-methylene moiety. The subsequent 1,3-shift of allylic hydrogen in **8′** takes place to afford the intermediates, 1,4-dihydro-1,10-phenanthrolin-4-ols **8**, which undergo dehydration to give 1,10-phenanthrolines **9**. More studies are underway to elucidate clearly the mechanism.

The structures of all new compounds (**8** and **9**) were easily determined on the basis of their ^{1}H NMR and IR spectra, together with elemental analyses. For example, in ^{1}H NMR spectrum of **8a**, two adjacent protons (amine and olefin protons) at 1- and 2-positions appeared at 8.88 and 6.72 ppm as doublets with coupling constant J = 4.0 Hz. When the H–D exchange of the amine proton (H-1) was carried out, the multiplicity of olefin proton (H-2) signal was changed to singlet. The data clearly show that the structure of the isolated intermediate is not **8′** but **8**.

It is noteworthy that we first succeeded in the isolation of the intermediates **8a**–**c**, which are the precursors of stable-aromatized final products, 1,10-phenanthrolines **9a**–**c**, and which seem to be

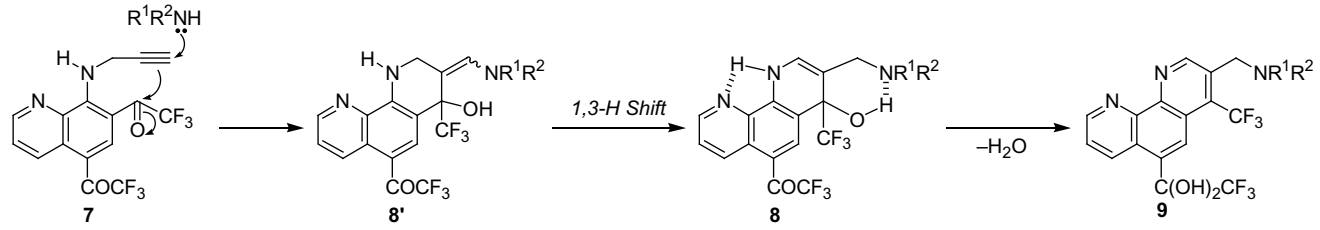


Scheme 3.

Table 1
Synthesis of 1,10-phenanthrolines **9** by the reaction of **7** with amines

Entry	1st step				2nd step					
	R^1R^2NH	Time (h)	Product	Yield (%)	TFA (equiv)	Temperature	Time (min)	Solvent	Product	Yield (%)
1	Me_2NH[a]	2	**8a**	98	54	Reflux	30	None	**9a**	62[b]
2	Et_2NH	2	**8b**	100	54	Reflux	30	None	**9b**	60[b]
3	Piperidine	1	**8c**	100	1	rt	30	$CHCl_3$	**9c**	63[b]
4	*t*-$BuNH_2$	4	—	—	5	rt	5	CH_3CN	**9d**	58[c]
5[d]	4-$MeOC_6H_4NH_2$	4	—	—	5	rt	5	CH_3CN	**9e**	51[c]
6[d]	4-$ClC_6H_4NH_2$	4	—	—	5	rt	5	CH_3CN	**9f**	58[c]

[a] Aqueous solution (50%) of dimethylamine was used.
[b] Isolated yields based on **8**.
[c] Isolated yields based on **7**.
[d] Triethylamine (0.5 equiv) was added.



Scheme 4.

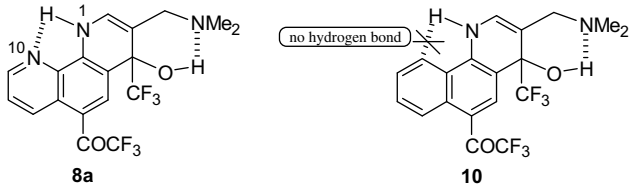


Figure 1.

unstable. This is a great difference in reactivity between the 8-quinoline system **7** and the naphthalene one **5**, as in the naphthalene system this type of intermediate, for example, **10** was not isolated and also not detected (Fig. 1).[12] Probably, it is thought that in **8a–c**, the additional hydrogen bond between H-1 and N-10, which cannot exist in the naphthalene system **10**, has contributed to the stability of **8a–c**, namely, has interrupted the dehydration accompanied by aromatization. We attempted the NMR experiment, where **8a** was solved in DMSO-d_6 as a solvent to disfavor the hydrogen bond between H-1 and N-10, allowed to stand at 33 °C, and the reaction progress was monitored by ^{1}H NMR. It was found that **8a** is gradually converted to **9a** under the above-described conditions as follows: conversion/standing time; 38%/3 days; 100%/7 days. It is thought that this result supports our speculation on stabilization of the intermediates **8a–c** by the intramolecular hydrogen bond.

In summary, we have demonstrated a simple and efficient access to CF_3-containing 1,10-phenanthrolines **9**, which are not easily obtained by other methods, via the pyridine-ring formation reaction of *N*-propargyl-8-quinolylamine derivative **7** with amines. Moreover, we succeeded in the isolation of the intermediates, 1,4-dihydro-1,10-phenanthrolin-4-ols **8a–c**. Our literature search did not reveal any previous reports on the isolation of 1,4-dihydro-1,10-phenanthrolin-4-ols.

Acknowledgments

We would like to thank the Japan Society for the Promotion of Science (JSPS), and the Centre National de la Recherche Scientifique (CNRS) for support of this research, the Direction des Relations Internationales (DRI) of the CNRS for travel funds (M.M.) and JSPS for a research fellowship (M.M.).

References and notes

1. (a) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha & Elsevier Biomedical: Tokyo, 1982; pp 1–240; (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197; (c) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993; pp 1–380; (d) Burger, K.; Wucherpfennig, U.; Brunner, E. *Adv. Heterocycl. Chem.* **1994**, *60*, 1–64.
2. (a) Katritzky, A. R.; Long, Q.-H.; Malhotra, N.; Ramanarayanan, T. A.; Vedage, H. *Synthesis* **1992**, 911–913; (b) Riesgo, E. C.; Jin, X.; Thummel, R. P. *J. Org. Chem.* **1996**, 3017–3022; (c) Okada, E.; Tsukushi, N. *Synthesis* **2000**, 499–501; (d) Gladiali, S.; Chelucci, G.; Mudadu, M. S.; Gastaut, M.-A.; Thummel, R. P. *J. Org. Chem.* **2001**, *66*, 400–405; (e) Elmaaty, T. A.; Castle, L. W. *Synthesis* **2006**, 1402–1404; (f) Chelucci, G.; Addis, D.; Baldino, S. *Tetrahedron Lett.* **2007**, *48*, 3359–3362; (g) Chelucci, G.; Baldino, S. *Tetrahedron Lett.* **2008**, *49*, 2738–2742; (h) Weitgenant, J. A.; Mortison, J. D.; O'Neill, D. J.; Mowery, B.; Puranen, A.; Helquist, P. *J. Org. Chem.* **2004**, *69*, 2809–2815.
3. (a) Kumar, R. S.; Arunachalam, S. *Polyhedron* **2007**, *26*, 3255–3262; (b) Liu, J.; Zheng, W.; Shi, S.; Tan, C.; Chen, J.; Zheng, K.; Ji, L. *J. Inorg. Biochem.* **2008**, *102*, 193–202; (c) Efthimiadou, E. K.; Katsarou, M. E.; Karaliota, A.; Psomas, G. *J. Inorg. Biochem.* **2008**, *102*, 910–920; (d) Mei, W.-J.; Wang, N.; Liu, Y.-J.; Ma, Y.-Z.; Wang, D.-Y.; Liang, B.-X. *Trans. Met. Chem.* **2008**, *33*, 499–503.
4. (a) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779–2782; (b) Durand, J.; Gladiali, S.; Erre, G.; Zangrando, E.; Milani, B. *Organometallics* **2007**, *26*, 810–818; (c) Glazer, E. C.; Magde, D.; Tor, Y. *J. Am. Chem. Soc.* **2007**, *129*, 8544–8551; (d) Mo, W.; Liu, H.; Xiong, H.; Li, M.; Li, G. *Appl. Catal. A* **2007**, *333*, 172–176; (e) Yu, X.; Lin, H.; Caia, Z.; Lin, H. *Tetrahedron Lett.* **2007**, *48*, 8615–8618.
5. Tzalis, D.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 3685–3688.
6. (a) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129–3170; (b) Chelucci, G.; Loriga, G.; Murineddub, G.; Pinnab, G. A. *Tetrahedron Lett.* **2003**, *43*, 3601–3604; (c) Elke, S. *Eur. J. Org. Chem.* **2003**, 1145–1152; (d) Sheen, W.-S.; Gau, H.-M. *Inorg. Chim. Acta* **2004**, *357*, 2279–2284; (e) Chelucci, G.; Muroni, D.; Manca, I. *J. Mol. Catal. A* **2005**, *225*, 11–14; (f) Roelfes, G.; Boersma, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 635–637.
7. (a) Liu, Y.-J.; Guan, X.-Y.; Wei, X.-Y.; He, L.-X.; Mei, W.-J.; Yao, J.-H. *Trans. Met. Chem.* **2008**, *33*, 289–294; (b) Kumar, R. S.; Arunachalam, S.; Periasamy, V. S.; Preethy, C. P.; Riyasdeen, A.; Akbarsha, M. A. *Polyhedron* **2008**, *27*, 1111–1120; (c) Rao, R.; Patra, A. K.; Chetana, P. R. *Polyhedron* **2008**, *27*, 1343–1352; (d) Gao, F.; Chao, H.; Weia, Y.-F.; Yuana, Y.-X.; Penga, B.; Chena, X.; Zhenga, K.-C.; Ji, L.-N. *Helv. Chim. Acta* **2008**, *91*, 395–410.
8. (a) Hojo, M.; Masuda, R.; Okada, E. *Tetrahedron Lett.* **1987**, *28*, 6199–6200; (b) Hojo, M.; Masuda, R.; Okada, E.; Miya, H. *Synthesis* **1989**, 870–873.
9. (a) Okada, E.; Tsukushi, N. *Synlett* **1999**, 210–212; (b) Okada, E.; Tsukushi, N.; Shimomura, N. *Synthesis* **2000**, 237–242.
10. Okada, E.; Tsukushi, N.; Otsuki, Y.; Nishiyama, S.; Fukuda, T. *Synlett* **1999**, 126–128 and references cited therein.
11. Okada, E.; Tsukushi, N.; Shimomura, N. *Synthesis* **2000**, 1822–1824 and references cited therein.
12. Okada, E.; Tone, H.; Tsukushi, N.; Otsuki, Y.; Takeuchi, H.; Hojo, M. *Heterocycles* **1997**, *45*, 339–346.
13. *A typical procedure for the synthesis of 1,4-dihydro-1,10-phenanthrolin-4-ols* **8a–c**: To a solution of **7** (187 mg, 0.5 mmol) in CH_3CN (5 mL) was added aqueous solution (50%) of dimethylamine (51 mg, 0.56 mmol), and the mixture was stirred at room temperature for 2 h. Evaporation of the solvent in vacuo gave practically pure **8a** (205 mg, 98%); mp 123–124 °C (dec) (*n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.48 (dd, 1H, J = 1.5, 8.5 Hz, H-7), 8.88 (br d, 1H, J = 4.0 Hz, NH), 8.81 (dd, 1H, J = 1.5, 4.0 Hz, H-9), 8.72 (s, 1H, H-5), 7.62 (dd, 1H, J = 4.0, 8.5 Hz, H-8), 7.76–7.28 (br, 1H, OH), 6.72 (d, 1H, J = 4.0 Hz, H-2), 3.99 (d, 1H, J_{gem} = 13.0 Hz, CH_2), 2.82 (d, 1H, J_{gem} = 13.0 Hz, CH_2), 2.31 (s, 6H, $N(CH_3)_2$); IR (KBr, cm^{-1}): 3402, 3094, 1697, 1676; Anal. Calcd for $C_{18}H_{15}F_6N_3O_2$: C, 51.56; H, 3.61; N, 10.02. Found: C, 51.63; H, 3.32; N, 9.89.
14. *A typical procedure for the synthesis of 1,10-phenanthrolines* **9a–c** *from 1,4-dihydro-1,10-phenanthrolin-4-ols* **8a–c**: A solution of **8a** (210 mg, 0.5 mmol) in CF_3CO_2H (2 mL) was stirred at reflux temperature for 30 min. The mixture was washed with saturated solution of Na_2CO_3, extracted with AcOEt, and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude product was purified by recrystallization from *n*-hexane and AcOEt to give **9a** (130 mg, 62%); mp 161–162 °C (*n*-hexane/AcOEt); ^{1}H NMR (500 MHz, CD_3CN): δ 9.38 (d, 1H, J = 8.5 Hz, H-7), 9.30 (s, 1H, H-2), 9.12 (d, 1H, J = 4.0 Hz, H-9), 8.79 (s, 1H, H-5), 7.95 (br s, 2H, OH), 7.74 (dd, 1H, J = 4.0, 8.5 Hz, H-8), 3.88 (s, 2H, CH_2), 2.28 (s, 6H, $N(CH_3)_2$); IR (KBr, cm^{-1}): 3352, 3115; Anal. Calcd for $C_{18}H_{15}F_6N_3O_2$: C, 51.56; H, 3.61; N, 10.02. Found: C, 51.83; H, 3.85; N, 9.75.
15. *A typical procedure for the one-pot synthesis of 1,10-phenanthrolines* **9d–f** *from N-propargyl-5,7-bis(trifluoroacetyl)-8-quinolylamine* **7**: To a solution of **7** (187 mg, 0.5 mmol) in CH_3CN (5 mL) were added *p*-anisidine (65 mg, 0.53 mmol) and triethylamine (25 mg, 0.25 mmol), and the mixture was stirred at room temperature for 4 h. Without work-up, to the reaction mixture was added CF_3CO_2H (0.19 mL, 2.6 mmol), and then it was further stirred for 5 min at room temperature. The mixture was washed with saturated solution of Na_2CO_3, extracted with AcOEt, and dried over Na_2SO_4. Evaporation of the solvent gave a

crude mixture which was subjected to column chromatography on silica gel eluting with *n*-hexane/AcOEt (1:1) to give **9e** (127 mg, 51%); mp 136–137 °C (dec) (*n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.44 (d, 1H, *J* = 9.0 Hz, H-7), 9.41 (s, 1H, H-2), 9.15 (d, 1H, *J* = 4.0 Hz, H-9), 8.88 (s, 1H, H-5), 7.68 (br s, 2H, OH), 7.66 (dd, 1H, *J* = 4.0, 9.0 Hz, H-8), 6.72 (d, 2H, *J* = 8.5 Hz, H_{arom}), 6.60 (d, 2H, *J* = 8.5 Hz, H_{arom}), 4.90–4.68 (br, 1H, NH), 4.81 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3); IR (KBr, cm^{-1}): 3415, 3363, 3115; Anal. Calcd for $C_{23}H_{17}F_6N_3O_3$: C, 55.54; H, 3.44; N, 8.45. Found: C, 55.75; H, 3.47; N, 8.23.