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A Novel One-Pot Pyrrole Synthesis via a Coupling–Isomerization–Stetter–Paal–Knorr Sequence†

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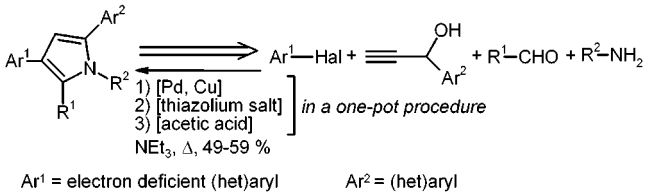
ABSTRACT

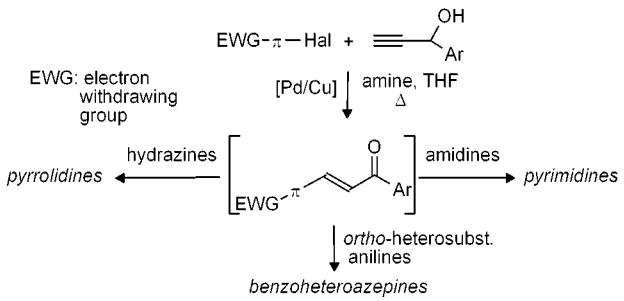


1,2,3,5-Tetrasubstituted pyrroles can be synthesized in good yields in a one-pot, three-step, four-component process by a coupling–isomerization–Stetter reaction–Paal–Knorr sequence of an electron-poor (hetero)aryl halide, a terminal propargyl alcohol, an aldehyde, and a primary amine. The structures of the 1,4-diketone 4f and the pyrrole 6b were additionally supported by X-ray structure analyses.

One-pot multicomponent processes have recently gained a considerable and steadily increasing academic, economic, and ecological interest because they address very fundamental principles of synthetic efficiency and reaction design.[1] Additionally, the prospect of extending one-pot reactions into combinatorial and solid-phase syntheses[1c,2] promises manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts, and even novel molecule based materials. With a palladium−copper-catalyzed domino cross-coupling−isomerization sequence of electron-poor halogen-substituted π-systems and 1-aryl prop-2-yn-1-ols furnishing 1,3-di(hetero)aryl enones (i.e., chalcones)[3] we have recently found a very efficient entry to three-component one-pot syntheses of pyrrolidines,[3] pyrimidines,[4] and 1,5-benzoheteroazepines[5] (Scheme 1).

Considering the mild reaction conditions, quite a number of generic structures of pharmaceutically relevant heterocyclic classes can be readily accessed. Among numerous heterocycles the pyrrole core has always been one of the most prominent since it constitutes important classes of natural products,[6] synthetic pharmaceuticals,[6c] and electrically conducting materials such as polypyrroles.[7] In particular, 1,2,3,5-tetrasubstituted pyrroles are highly biologically active and have proven to display antibacterial,[8] antiviral (also anti-HIV-1),[9] antiinflammatory,[10] and antioxidant[11] activity and to inhibit cytokine-mediated diseases.[12] Thus, applying our

Scheme 1. One-Pot Syntheses of Pyrazolines, Pyrimidines, and Benzoheteroazepines Based upon a Coupling−Isomerization Sequence



† Dedicated to Prof. Dr. Rolf Gleiter on the occasion of his 65th birthday.
‡ X-ray crystal structure analysis.

(1) (a) Ugi, I.; Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (b) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (c) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, *366*.
(2) Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1.
(3) Müller, T. J. J.; Ansorge, M.; Aktah, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1253.
(4) Müller, T. J. J.; Braun, R.; Ansorge, M. *Org. Lett.* **2000**, *2*, 1967.

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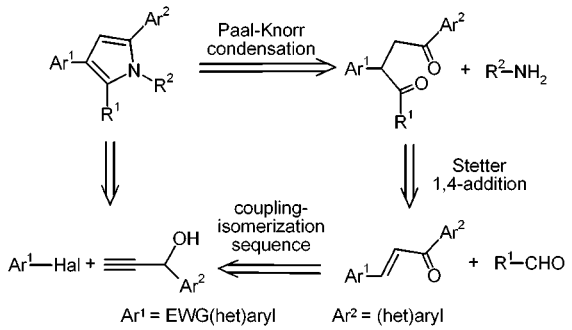
coupling−isomerization concept toward the synthesis of pyrroles it can be easily envisioned that 1,2,3,5-substituted pyrroles should be accessible by combining a Stetter reaction, furnishing the 1,4-diketones,[13] and a subsequent Paal−Knorr cyclocondensation (Scheme 2).[6a,b,d] Here, we wish to communicate first synthetic studies on a novel one-pot pyrrole synthesis based upon a coupling−isomerization−Stetter−Paal−Knorr sequence.

Scheme 2. Retrosynthetic Concept for a Four-Component Pyrrole Synthesis



First, we tested the compatibility of the Stetter addition of aldehydes to the in situ formed chalcone functionality. Thus, we submitted *p*-bromo benzonitrile (**1a**) or 2-bromo pyridine (**1b**), (hetero)aryl propynols **2**,[14] and after some reaction time (hetero)aryl aldehydes **3** in the presence of a thiazolium salt to the reaction conditions of the Sonogashira coupling in boiling triethylamine.[15] In all cases the beige to yellow 1,2,4-tri(hetero)aryl-1,4-diketones **4** were obtained in 75−88% yield (Table 1).[16]

The NMR spectroscopic data support the formation of the 1,4-diketones, in particular, in the ^{1}H NMR spectra of **4** by the indicative appearance of the ABM-spin system with the characteristic geminal and vicinal coupling constants for the methylene group resonances (^2J = 18.0, ^3J = 4.3, ^3J = 9.6 Hz) and the vicinal coupling constants for the methine resonances (^3J = 4.4, ^3J = 9.6 Hz). Furthermore, the structure of **4** was unambiguously supported by an X-ray crystal structure analysis (Figure 1) of compound **4f**[17] (Table 1, entry 6).

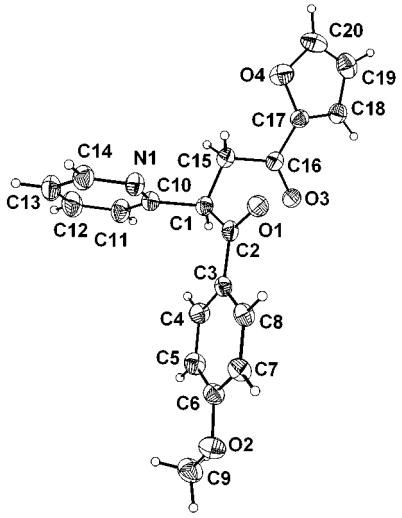


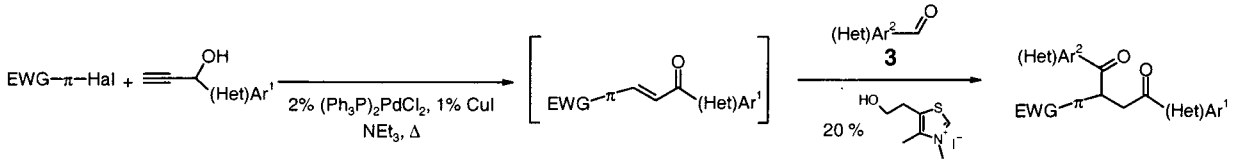
Figure 1. ORTEP plot of compound **4f**.

Finally, we have combined the one-pot coupling−isomerization−Stetter reaction with the fourth step, i.e., a Paal−Knorr pyrrole reaction for designing a novel four-component pyrrole synthesis. Thus, applying *p*-bromo benzonitrile (**1a**) and 1-phenyl propyn-1-ol (**2a**) to the conditions of the chalcone formation, after some reaction time adding (hetero)-

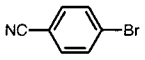
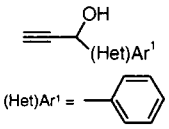
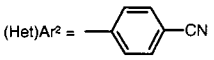
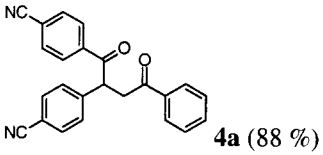
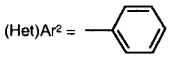
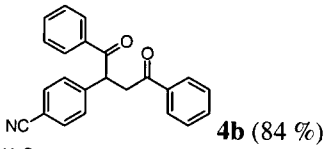
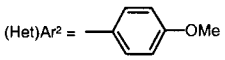
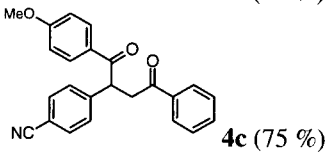
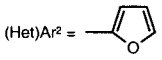
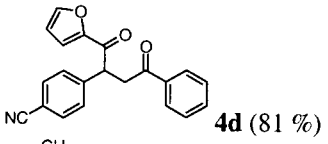
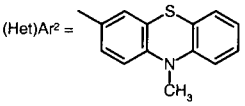
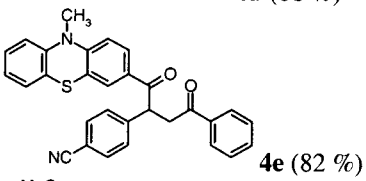
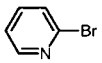
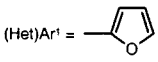
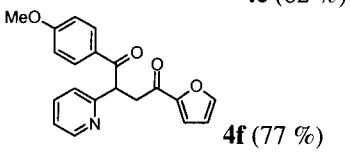
(5) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2000**, *2*, 4181.
(6) For excellent reviews, see: (a) Gossauer, A. *Die Chemie der Pyrrole*; Springer-Verlag: Berlin, Heidelberg, New York, 1974. (b) Gossauer, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R., Ed.; G. Thieme Verlag: Stuttgart, 1994; Bd. E6a, p 556. (c) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1996; Vol. 2, p 207. (d) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1996; Vol. 2, 119. (e) Fürstner, A. *Synlett* **1999**, 1523.
(7) For an interesting review, see: MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27.
(8) Daidone, G.; Maggio, B.; Schillaci, D. *Pharmazie* **1990**, *45*, 441.
(9) (a) Almerico, A. M.; Diana, P.; Barraja, P.; Dattolo, G.; Mingoia, F.; Loi, A. G.; Scintu, F.; Milia, C.; Puddu, I.; La Colla, P. *Farmaco* **1998**, *53*, 33. (b) Almerico, A. M.; Diana, P.; Barraja, P.; Dattolo, G.; Mingoia, F.; Putzolu, M.; Perra, G.; Milia, C.; Musiu, C.; Marongiu, M. E. *Farmaco* **1997**, *52*, 667.
(10) (a) Kimura, T.; Kawara, A.; Nakao, A.; Ushiyama, S.; Shimozato, T.; Suzuki, K. PCT Int. Appl. WO 0001688 A1 20000113, 2000. (b) Kaiser, D. G.; Glenn, E. M. *J. Pharm. Sci.* **1972**, *61*, 1908.
(11) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J.-M. *Eur. J. Med. Chem.* **1999**, *34*, 991.
(12) (a) Kawai, A.; Kawai, M.; Murata, Y.; Takada, J.; Sakakibara, M. PCT Int. Appl. WO 9802430 A1 19980122, 1998. (b) De Laszlo, S. E.; Liverton, N. J.; Ponticello, G. S.; Selnick, H. G.; Mantlo, N. B. U.S. Patent 5837719 A 19981117, 1998. (c) De Laszlo, S. E.; Liverton, N. J.; Ponticello, G. S.; Selnick, H. G.; Mantlo, N. B. U.S. Patent 5792778 A 19980811, 1998. (d) De Laszlo, S. E.; Chang, L. L.; Kim, D.; Mantlo, N. B. PCT Int. Appl. WO 9716442 A1 19970509, 1997.
(13) (a) Stetter, H.; Kuhlmann, H.; Haese, W. *Org. Synth.* **1987**, *65*, 26. (b) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407. (c) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.
(14) The propynols **5** were synthesized according to Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.

(15) **Typical Procedure (4d).** (Table 1, entry 4) A magnetically stirred solution of 182 mg (1.00 mmol) of 4-bromo benzonitrile (**1a**), 139 mg (1.05 mmol) of 1-phenyl propyn-1-ol (**2a**), 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 2 mg (0.01 mmol) of CuI in 5 mL of degassed triethylamine under nitrogen was heated to reflux temperature for 16 h. After the mixture cooled to room temperature, 115 mg (1.20 mmol) of furfural (**3d**) and 57 mg (0.2 mmol) of the thiazolium salt were added, and the reaction mixture was heated to reflux temperature for 8 h. After being allowed to cool the mixture was filtered, solvents were removed from the filtrate in vacuo, and the residue was recrystallized from ethanol to give 261 mg (81%) of analytically pure **4d** as light yellow crystals, mp 179 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.36 (dd, J = 4.3, 18.0 Hz, 1 H), 4.13 (dd, J = 9.6, 18.0 Hz, 1 H), 5.21 (dd, J = 4.4, 9.6 Hz, 1 H), 6.53 (dd, J = 1.7, 3.6 Hz, 1 H), 7.27 (m, 1 H), 7.42−7.63 (m, 8 H), 7.96 (d, J = 7.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.5 (CH_2), 48.8 (CH), 111.8 (C_{quat}), 112.9 (CH), 118.8 (CH), 118.9 (C_{quat}), 128.4 (CH), 129.0 (CH), 129.5 (CH), 133.0 (CH), 133.8 (CH), 136.4 (C_{quat}), 143.9 (C_{quat}), 147.2 (CH), 152.2 (C_{quat}), 186.9 (C_{quat}), 197.3 (C_{quat}). MS (70 eV, *m*/*z* %): 329 (M^+, 17), 224 ($M^+ - C_6H_5CO$, 11), 105 (C_6H_5CO, 40), 95 (C_4H_3CO, 100). Anal. Calcd for $C_{21}H_{15}NO_3$ (329.4): C, 76.58; H, 4.59; N, 4.25. Found: C, 76.54; H, 4.69; N, 4.19.
(16) All compounds have been fully characterized spectroscopically and by correct elemental analysis or HRMS, respectively

Table 1. Three-Component 1,4-Diketone Synthesis Based upon a Coupling−Isomerization−Stetter−Acylation Sequence[a]



1 **2** **4** (75-88 %)

Entry	EWG-π-Hal **1**	Propargyl alcohol **2**	Aldehyde **3**	1,4-Diketone **4** (Yield %)[b]
1	 **1a**	 **2a**	 **3a**	 **4a** (88 %)
2	**1a**	**2a**	 **3b**	 **4b** (84 %)
3	**1a**	**2a**	 **3c**	 **4c** (75 %)
4	**1a**	**2a**	 **3d**	 **4d** (81 %)
5	**1a**	**2a**	 **3e**	 **4e** (82 %)
6	 **1b**	 **2b**	**3c**	 **4f** (77 %)

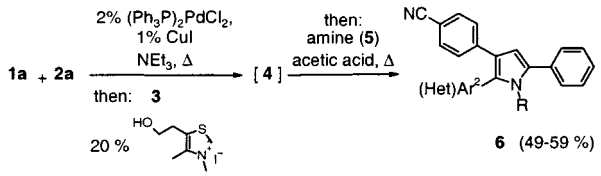
[a] Reaction conditions: 1.0 equiv of the (hetero)aryl halide **1**, 1.05 equiv of the propargyl alcohol **2**, 0.02 equiv of $(Ph_3P)_2PdCl_2$, 0.01 equiv of CuI, 1.2 equiv of the aldehyde **3**, 0.2 equiv of the thiazolium salt, and NEt_3 (5 mL/mmol halide). [b] Yields refer to isolated yields of compounds **4** after recrystallization estimated to be 95% pure as determined by NMR spectroscopy and elemental analysis.

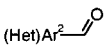
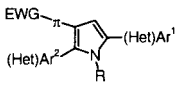
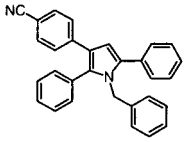
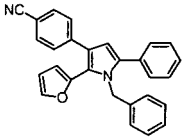
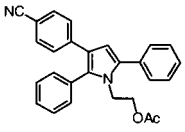
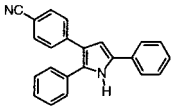
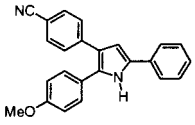
aryl aldehydes **3** in the presence of a thiazolium salt to the reaction mixture, and finally adding primary amines **5** or ammonium chloride in the presence of acetic acid, the pyrroles **6** were formed in moderate yields as a result of a coupling−isomerization−Stetter−Paal−Knorr sequence (Table 2).[18,16]

The formation of the pyrroles is strongly supported by the NMR spectra, in particular, in the ^{13}C NMR spectra of **6** by the indicative appearance of the quaternary C-3 resonance at δ 108 and the C-4 methine carbon signal at δ 109 of the pyrrole core. In addition, the structure of **6** was unambiguously supported by an X-ray crystal structure analysis (Figure 2) of compound **6b** (Table 2, entry 2).[17]

In conclusion, we could show that the mild reaction conditions of the coupling−isomerization sequence of electron-poor (hetero)aryl halides with 1-aryl propargyl alcohols giving rise to chalcones can be extended to a one-pot three-component synthesis of 1,4-diketones (Stetter reaction) and, even further, to a one-pot four-component pyrrole synthesis in the sense of a coupling−isomerization−Stetter−Paal−Knorr sequence. Further studies directed to extend these one-

Table 2. Four-Component Pyrrole Synthesis Based upon a Coupling−Isomerization−Stetter−Paal−Knorr Sequence[a]



Entry	3	Amine 5	Pyrrole 6 (Yield %)[b]
			
1	**3b**	R = Bn **5a**	 **6a** (49 %)
2	**3d**	**5a**	 **6b** (55 %)
3	**3c**	R = **5b**	 **6c**[c] (57 %)
4	**3b**	R = **5c**	 **6d**[d] (59 %)
5	**3c**	$NH_4^+Cl^-$ **5d**	 **6e** (56 %)

[a] Reaction conditions: 1.0 equiv of the aryl halide **1a**, 1.05 equiv of the propargyl alcohol **2a**, 0.02 equiv of $(Ph_3P)_2PdCl_2$, 0.01 equiv of CuI, 1.2 equiv of the aldehyde **3**, 0.2 equiv of the thiazolium salt, NEt_3 (2.5 mL/mmol halide), 1.2 equiv of the amine **5**, and acetic acid (2.5 mL/5 mL amine). [b] Yields refer to isolated yields of compounds **6** after recrystallization estimated to be 95% pure as determined by NMR spectroscopy and elemental analysis. [c] The acetylation occurred under the reaction conditions. [d] Nitrogen was transferred from glycine amide.

pot heterocycle syntheses to pharmaceutically and electronically interesting systems such as oligopyrroles are currently underway.

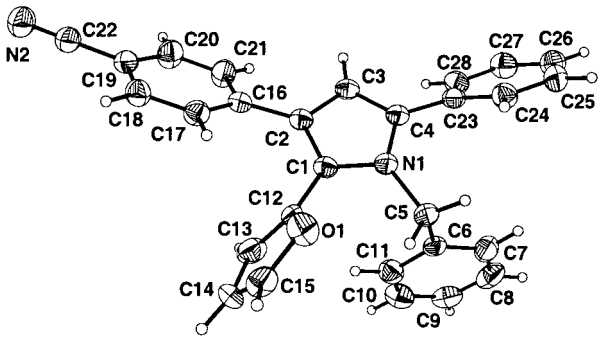


Figure 2. ORTEP plot of compound **6b**.

Acknowledgment. The financial support of the Fonds der Chemischen Industrie and the Dr.-Otto-Röhm Gedächtnisstiftung is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of compounds **4** and **6**. Tables of data collection parameters, bond lengths and angles, positional and thermal parameters, and least-squares planes for **4f** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-167866 (**4f**) and no. CCDC-167867 (**6b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: + 44-1223/336-033. E-mail: deposit@ccdc.cam.ac.uk).

(18) **Typical Procedure (6b).** (Table 2, entry 2) According to ref 15 the coupling−isomerization−Stetter sequence was performed with 364 mg (2.00 mmol) of **1a**, 278 mg (2.1 mmol) of **2a**, 44 mg (0.04 mmol) of $Pd(PPh_3)_2Cl_2$, 4 mg (0.02 mmol) of CuI, 230 mg (2.40 mmol) of **3d**, and 114 mg (0.4 mmol) of thiazolium salt in 4 mL of triethylamine. After the mixture cooled, 857 mg (8 mmol) of benzylamine (**5a**) and 2.5 mL of acetic acid were added, and the mixture was heated to reflux temperature for 5 d. After cooling and aqueous workup the residue was chromatographed on silica gel (ethyl acetate/hexanes 1:6), and the residue was recrystallized from ethanol to give 444 mg (55%) of analytically pure **6b** as colorless crystals, mp 104−105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.14 (s, 2 H), 6.15 (d, J = 3.1 Hz, 1 H), 6.36 (dd, J = 1.8, 3.2 Hz, 1 H), 6.55 (s, 1 H), 6.81−6.84 (m, 2 H), 7.18−7.25 (m, 3 H), 7.31−7.36 (m, 7 H), 7.43 (d, J = 1.4 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 48.9 (CH_2), 108.8 (C_{quat}), 109.2 (CH), 111.2 (CH), 112.1 (CH), 119.4 (C_{quat}), 122.3 (C_{quat}), 124.6 (C_{quat}), 125.9 (CH), 127.1 (CH), 127.6 (CH), 127.9 (CH) 128.5 (CH), 128.55 (CH), 129.1 (CH), 132.1 CH), 132.5 (C_{quat}), 137.4 (C_{quat}), 138.6 (C_{quat}), 140.6 ($C_{quat.}$, 143.0 (CH), 145.1 ($C_{qua.}$). MS (70 eV, m/z(%): 400 (M^+, 86), 309 ($M^+ - C_6H_5CH_2$, 100), 91 ($C_6H_5CH_2$, 32). Anal. Calcd for $C_{28}H_{20}N_2O$ (400.5): C, 83.98; H, 5.03; N, 7.00. Found: C, 83.88; H, 4.96; N, 6.97.