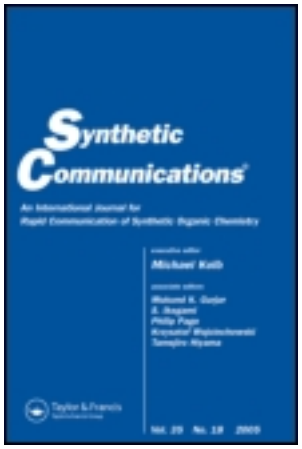

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An Efficient Four-Component Synthesis of Multisubstituted Pyrano[2,3-c]pyrazole

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AN EFFICIENT FOUR-COMPONENT SYNTHESIS OF MULTISUBSTITUTED PYRANO[2,3-c]PYRAZOLE

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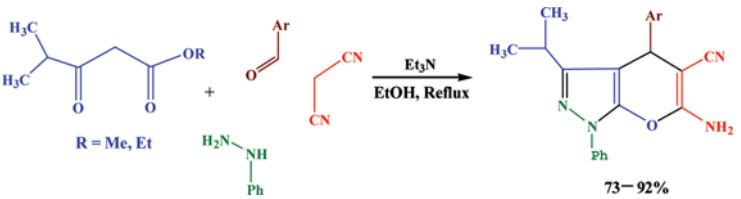
GRAPHICAL ABSTRACT



Abstract *A series of substituted pyrano[2,3-c]pyrazole derivatives were synthesized by a one-pot reaction of methyl 4-methyl-3-oxovalerate, phenylhydrazine, aromatic aldehyde, and malononitrile in ethanol with catalysis by triethylamine. The title compounds were obtained in good to excellent yields. A possible mechanism for this reaction was proposed.*

Keywords Aldehyde; malononitrile; methyl methyl-3-oxovalerate; multicomponent reaction; one-pot synthesis; pyrano[2,3-c]pyrazole

INTRODUCTION

Multicomponent reactions (MCRs) have been widely used in synthetic, combinatorial, and medicinal chemistry as an effective method to construct multiple bonds in a single operation.[1] These reactions are atom-efficient processes and incorporate the essential parts of the starting materials into the final product. MCRs are powerful tools in the modern drug-discovery process and allow the fast, automated, and high-throughput generation of organic compounds.[2] In the past decade, there has been tremendous development in three- and four-component reaction, and much effort has been devoted to the development of a new MCRs.[3] The application of MCRs is increasing rapidly because of the simplicity of reaction, less pollution, and short reaction times. The development of simple synthetic routes for widely used organic compounds from readily available reagents is a challenging work in organic synthesis.[4]

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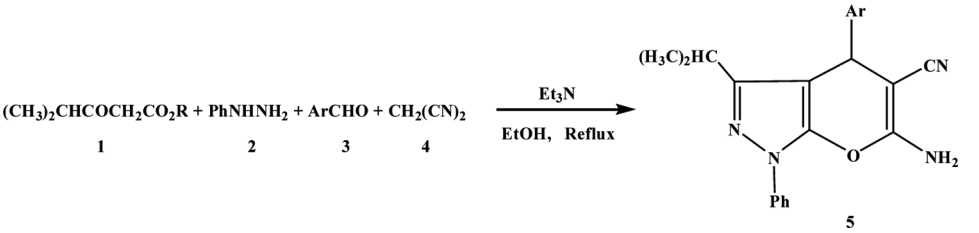


Scheme 1. One-pot synthesis of substituted pyrano[2,3-c]pyrazole derivatives (**5a–5j**).

Pyrano[2,3-c]pyrazoles have been used as intermediates in the synthesis of heterocycles because of their important practical applicability.[5] Also, many methods have been reported for the formation of pyrano[2,3-c]pyrazole, and this moiety has been widely used in medicinal chemistry because of its diverse biological activities and pharmacological properties,[6] such as anticancer,[7] anti-inflammatory,[8] and antimicrobial properties.[9]

Therefore, new routes for the synthesis of these molecules have attracted considerable attention in the search for a rapid entry to these heterocycles. Generally, 6-amino-4H-pyrano[2,3-c]pyrazoles were synthesized by the reaction of arylidene-malononitriles with 3-methylpyrazol-5-one or condensation of 4-arylidenepyrazol-5-ones with malononitrile via a two-step process.[5c] Recently, a few reports have described the synthesis of substituted pyrano[2,3-c]pyrazole derivatives via MCRs of aldehyde, malononitrile, and 3-methy-2-pyrazolin-5-one in the presence of piperidine,[10] $KF \cdot 2H_2O$,[11] or D,L-proline.[12] In addition, a three-component

Table 1. Reaction times and yields of compounds **5a–5j**

Entry	R	Ar	Product	Time (min)	Yield (%)[a]
1	CH_3	C_6H_5	**5a**	10	81
2	CH_3	*p*-MeC_6H_4	**5b**	10	90
3	CH_3	*p*-$MeOC_6H_4$	**5c**	10	92
4	CH_3	*p*-ClC_6H_4	**5d**	8	84
5	CH_3	*p*-rC_6H_4	**5e**	6	80
6	CH_3	*p*-FC_6H_4	**5f**	6	80
7	CH_3	*p*-$O_2NC_6H_4$	**5g**	8	84
8	CH_3	*p*-HOC_6H_4	**5h**	8	90
9	CH_3	3-Pyridyl	**5i**	6	87
10	CH_3	1-Naphthyl	**5j**	8	85
11	CH_3CH_2	C_6H_5	**5a**	15	73
12	CH_3CH_2	*p*-MeC_6H_4	**5b**	15	80
13	CH_3CH_2	*p*-$MeOC_6H_4$	**5c**	15	82
14	CH_3CH_2	*p*-ClC_6H_4	**5d**	15	75
15	CH_3CH_2	*p*-rC_6H_4	**5e**	15	74
16	CH_3CH_2	*p*-FC_6H_4	**5f**	15	75
17	CH_3CH_2	*p*-$O_2NC_6H_4$	**5g**	15	76
18	CH_3CH_2	*p*-HOC_6H_4	**5h**	15	84
19	CH_3CH_2	3-Pyridyl	**5i**	15	80
20	CH_3CH_2	1-Naphthyl	**5j**	15	76

[a]Yields of the isolated products.

base[13] or electrocatalyzed[14] reaction of aldehydes, malonodinitrile, and pyrazolin-5-one was a simple protocol for preparation of the diverse pyrano[2,3-c]pyrazoles. Although there is a developed four-component synthetic method for some 6-amino-2,4-dihydro-pyrano-[2,3-c]pyrazol-5-carbo-nitriles,[15] the method was unable to extend it to phenyl hydrazine as a reactant. Therefore, improved and high-efficiency syntheses for a novel multisubstituted pyrano[2,3-c]pyrazoles are in demand.

As part of our current study in the development of new synthetic methods in heterocyclic chemistry and our interest in pyrazole-based MCRs, herein we describe an efficient synthesis of substituted pyrano[2,3-c]pyrazols via a one-pot, four-component reaction catalyzed by triethylamine (Scheme 1). The reaction has been carried out by refluxing the mixture of four reactants at 80 °C for 6–15 min. The yields of products **5a**–**5j** are presented in Table 1. The ^{1}H NMR spectra of products **5a**–**5j** clearly indicated the formation of pyrano[2,3-c]pyrazoles **5**.

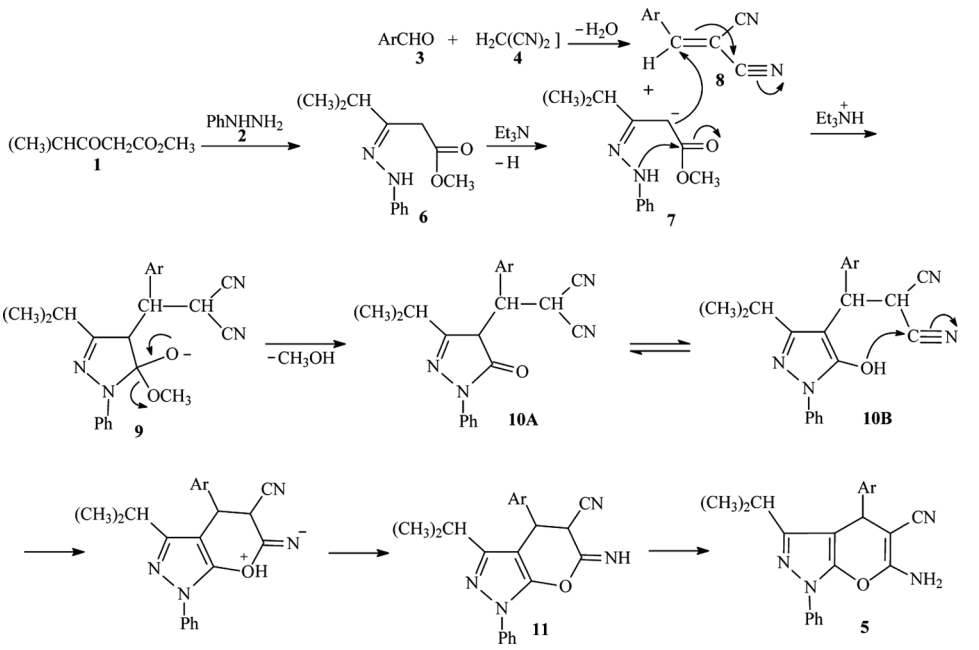
RESULTS AND DISCUSSION

The corresponding products **5** were obtained in good yields (73–92%) through the reaction of **1, 2, 3,** and **4**. As shown in Table 1, the yields were slightly higher when electron-withdrawing groups (such as NO_2 and Cl group) exist in aromatic aldehydes rather than electron-donating groups. It must be pointed out that the reaction requires less reaction time (6–8 min) for formation of corresponding products when electron-withdrawing groups exist in aromatic aldehydes.

Significant differences in yields of the same products were observed by using **1a** and **1b** reactants, respectively. When methyl 4-methyl-3-oxovalerate **1a** was used as a reactant instead of ethyl 4-methyl-3-oxovalerate **1b**, the yields of products **5a**–**5j** increased by 6–10% (Table 1).

The structures of products **5a**–**5j** were deduced on the basis of infrared (IR), mass (MS), ^{1}H NMR, and elemental analyses. The identification of representative compound **5i** is discussed as an example. The mass spectrum of compound **5i** displayed highly abundant m/z 358 and m/z 380 ions that correspond to adduct molecular ion peaks $[M+H]^+$ and $[M+Na]^+$, respectively. Characteristic absorption bands of CN group at 2189 cm^{-1} and NH_2 group at 3357, 3133 cm^{-1} were observed in the IR spectrum of **5i**. The ^{1}H NMR spectrum of compound **5i** showed a broad peak at 7.29 ppm, which belongs to two H's of the NH_2 group. A sharp singlet appeared at 4.83 ppm assigned to one H of CH in pyrano ring. The H in two Me of isoproply group appeared at 0.81 and 1.04 ppm, respectively, coupled with the H of CH (2.43 ppm, septet), which was confirmed by coupling constant ($J = 7.2$ Hz). According to the structure of products, we assume that the different signals for Me were related to the stereogenic center in products.

The formation of compounds **5a**–**5j** is explained as follows (Scheme 2). At first, intermediates **6** and **8** were formed by the condensation of phenylhydrazine (**2**) with methyl 4-methyl-3-oxovalerate (**1a**) and arylaldehydes (**3**) with malononitrile (**4**), respectively. Subsequent Michael reaction between intermediate **6** and intermediate **8** and intramolecular reaction between NH and C=O occur simultaneously, leading to intermediate **9**. Furthermore, after the removal of methanol from **9**, the subsequent intramolecular cyclization in intermediate **10B** by the nucleophilic attack of OH group to the carbon of CN moiety affords the final product **5**.



Scheme 2. Proposed mechanism for the formation of **5a–5j**.

In summary, we have developed a new, convenient, one-pot method for the synthesis of 6-amino-4-aryl-3-isopropyl-1-phenyl-4H-pyrano[2,3-c]pyrazole-5-carbonitrile via a four-component reaction using triethylamine as a catalyst. This method has the advantages of good yields, easy workup, and short reaction times, which make it a useful and attractive process for the synthesis of these types of compounds.

EXPERIMENTAL

The melting point was determined on a Buchi B2540 microscopic melting apparatus. The ^{1}H NMR spectrum was recorded on a Varian Inova 400 instrument with dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as internal standard. Infrared (IR) spectrum was measured with a Bruker Equinox55 spectrometer as KBr pellets. The elemental analyses was performed with a Perkin-Elmer EA-1110 elemental analyses instrument. Mass spectral (MS) data were obtained on an MDS mass spectrometer. All chemicals were obtained from commercial suppliers and used without further purification.

General Procedure for the Syntheses of 6-Amino-4-aryl-3-isopropyl-1-phenyl-4H-pyrano[2,3-c]pyrazole-5-carbonitrile

A solution of methyl 4-methyl-3-oxovalerate **1a** (0.300 g, 2 mmol) and phenylhydrazine **2** (0.225 g, 2 mmol) was refluxed in absolute ethanol (20 ml) for 2 min. Then, phenyl aldehyde **3** (0.221 g, 2 mmol), malononitrile **4** (0.138 g, 2 mmol), and triethylamine (2–3 drops) were added to the mixture, and the heating continued

for 5 to 10 min. The reaction system was cooled to room temperature. The precipitate that formed was filtered off, washed with ethanol, and recrystallized from ethanol-DMF to afford the pure product.

Data

Compound 5a. White crystals; mp 234–236 °C. IR (KBr, ν/cm^{-1}): 3455, 3320 (NH_2, br), 2200 (C≡N), 1658, 1590, 1517 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): $\delta = 0.82$ (d, 3H, $J = 7.2$ Hz, CH_3), 1.03 (d, 3H, $J = 7.2$ Hz, CH_3), 2.46 (sep, 1H, $J = 7.2$ Hz, CH), 4.36 (s, 1H, CH), 7.18 (s, 2H, NH_2), 7.18–7.82 (m, 10H, Ar-H). MS, m/z (%): 357 ($[M+H]^+$, 100), 379 ($[M+Na]^+$, 38). Anal. calcd. for $C_{22}H_{20}N_4O$ (356.43) C, 74.14; H, 5.66; N, 15.72. Found: C, 74.01; H, 5.46; N, 15.67.

Compound 5b. White crystals; mp 247–248 °C. IR (KBr, ν/cm^{-1}): 3466, 3321 (NH_2, br), 2201 (C≡N), 1661, 1593, 1515 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3 H, $J = 7.2$ Hz, CH_3), 1.03 (d, 3H, $J = 7.2$ Hz, CH_3), 2.50 (sep, 1H, $J = 7.2$ Hz, CH), 2.29 (s, 3H, CH_3), 4.66 (s, 1H, CH), 7.14 (s, 2H, NH_2), 7.11 (d, $J = 8.8$ Hz, 2H, p-H_3C-C_6H_4), 7.12–7.50 (m, 5H, C_6H_5), 7.80 (d, $J = 8.8$ Hz, 2H, p-H_3C-C_6H_4). MS, m/z (%): 371 ($[M+H]^+$, 100), 393 ($[M+Na]^+$, 50). Anal. calcd. for $C_{23}H_{22}N_4O$ (370.45): C, 74.57; H, 5.99; N, 15.12. Found: C, 74.44; H, 5.94; N, 15.02.

Compound 5c. White crystals; mp 270–272 °C. IR (KBr, ν/cm^{-1}): 3460, 3322 (NH_2, br), 2201 (C≡N), 1660, 1592, 1516 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): $\delta = 0.84$ (d, 3H, $J = 7.2$ Hz, CH_3), 1.01 (d, 3H, $J = 7.2$ Hz, CH_3), 2.46 (sep, 1H, $J = 7.2$ Hz, CH), 3.74 (s, 3H, OCH_3), 4.66 (s, 1H, CH), 7.13 (s, 2H, NH_2), 6.90 (d, $J = 8.4$ Hz, 2H, p-H_3CO-C_6H_4), 7.16 (d, $J = 8.4$ Hz, 2H, p-H_3CO-C_6H_4), 7.32–7.80 (m, 5H, C_6H_5). MS, m/z (%): 387 ($[M+H]^+$, 50), 409 ($[M+Na]^+$, 100). Anal. calcd. for $C_{23}H_{22}N_4O_2$(386.45): C, 71.48; H, 5.74; N, 14.50. Found: C, 71.28; H, 5.69; N, 14.43.

Compound 5d. White crystals; mp 268–270 °C. IR (KBr, ν/cm^{-1}): 3456, 3324 (NH_2, br), 2200 (C≡N), 1661, 1591, 1517 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): $\delta = 0.84$ (d, 3H, $J = 6.8$ Hz, CH_3), 1.04 (d, 3H, $J = 6.8$ Hz, CH_3), 2.49 (sep, 1H, $J = 6.8$ Hz, CH), 4.77 (s, 1H, CH), 7.23 (s, 2H, NH_2), 7.30 (d, $J = 8.4$ Hz, 2H, p-Cl-C_6H_4), 7.33–7.80 (m, 5H, C_6H_5), 7.39 (d, $J = 8.4$ Hz, 2H, p-Cl-C_6H_4). MS, m/z (%): 413 ($[M+Na]^+$, 60), 391 ($[M+H]^+$, 80). Anal. calcd. for $C_{22}H_{19}ClN_4O$ (390.87): C, 67.60; H, 4.90; N, 14.33. Found: C, 67.34; H, 4.79, N, 14.10.

Compound 5e. White crystals; mp 262–264 °C; IR (KBr, ν/cm^{-1}): 3452, 3324 (NH_2, br), 2197 (C≡N), 1660, 1591, 1517 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): $\delta = 0.86$ (d, 3H, $J = 7.2$ Hz, CH_3), 1.04 (d, 3H, $J = 7.2$ Hz, CH_3), 2.45 (sep, 1H, $J = 7.2$ Hz, CH), 4.75 (s, 1H, CH), 7.23 (s, 2H, NH_2), 7.26 (d, $J = 8.8$ Hz, 2H, p-Br-C_6H_4), 7.33–7.53 (m, 5H, C_6H_5), 7.81 (d, $J = 8.8$ Hz, 2H, p-Br-C_6H_4). MS, m/z (%): 459 ($[M+2+Na]^+$, 40), 457 ($[M+Na]^+$, 36), 437 ($[M+2+H]^+$, 100), 435 ($[M+H]^+$, 80). Anal. calcd. for $C_{22}H_{19}BrN_4O$ (435.32): C, 60.70; H, 4.40; N, 12.87. Found: C, 60.47; H, 4.32, N, 13.04.

Compound 5f. White crystals; mp 262–263 °C. IR (KBr, ν/cm^{-1}): 3471, 3358 (NH_2, br), 2198 (C≡N), 1681, 1601, 1591 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): δ = 0.84 (d, 3H, J = 7.2 Hz, CH_3), 1.04 (d, 3H, J = 7.2 Hz, CH_3), 2.45 (sep, 1H, J = 7.2 Hz, CH), 4.76 (s, 1H, CH), 7.17 (s, 2H, NH_2), 7.15 (d, J = 8.4 Hz, 2H, p-F-C_6H_4), 7.31–7.80 (m, 5H, C_6H_5), 7.31 (d, J = 8.4 Hz, 2H, p-F-C_6H_4). MS, m/z (%): 398 ($[M+2+Na]^+$, 10), 397 ($[M+Na)^+$, 20), 376 ($[M+1+H]^+$, 38), 375 ($[M+H]^+$, 100). Anal. calcd. for $C_{22}H_{19}FN_4O$ (374.42): C, 70.57; H, 5.11; N, 14.96. Found: C, 70.38; H, 5.08; N, 14.87.

Compound 5g. Yellow crystals; mp 281–283 °C. IR (KBr, ν/cm^{-1}): 3425, 3331 (NH_2, br), 2200 (C≡N), 1684, 1600, 1517 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): δ = 0.85 (d, 3H, J = 7.2 Hz, CH_3), 1.05 (d, 3H, J = 7.2 Hz, CH_3), 2.43 (sep, 1H, J = 7.2 Hz CH), 4.97 (s, 1H, CH), 7.32–7.61 (m, 5H, C_6H_5), 7.35 (s, 2H, NH_2), 7.80 (d, J = 8.8 Hz, 2H, p-O_2N-C_6H_4), 8.23 (d, J = 8.8 Hz, 2H, p-O_2N-C_6H_4). MS, m/z (%): 424 ($[M+Na]^+$, 100), 402 ($[M+H]^+$, 25). Anal. calcd. for $C_{22}H_{19}N_5O_3$(401.42): C, 65.83; H, 4.77; N, 17.45. Found: C, 65.68; H, 4.70; N, 17.32.

Compound 5h. White crystals; mp 261–263 °C. IR (KBr, ν/cm^{-1}): 3398 (OH), 3325, 3214 (NH_2, br), 2177 (C≡N), 1658, 1594, 1515 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): δ = 0.85 (d, 3H, J = 6.8 Hz, CH_3), 1.02 (d, 3H, J = 6.8 Hz, CH_3), 2.47 (sep, 1H, J = 7.2 Hz, CH), 4.59 (s, 1 H, CH), 6.70 (d, 2H, J = 8.4 Hz, p-HO-C_6H_4), 7.03 (d, 2H, J = 8.4 Hz, p-HO-C_6H_4), 7.09 (s, 2H, NH_2), 7.31–7.79 (m, 5H, C_6H_5), 9.33 (s, 1 H, OH). MS, m/z (%): 395 ($[M+Na]^+$), 373 ($[M+H]^+$). Anal. calcd. for $C_{22}H_{20}N_4O_2$ (372.43): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.78; H, 5.37; N, 14.98.

Compound 5i. White crystals; mp 250–252 °C. IR (KBr, ν/cm^{-1}): 3357, 3133 (NH_2, br), 2189 (C≡N), 1660, 1582, 1515 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): δ = 0.81 (d, 3H, J = 6.8 Hz, CH_3), 1.04 (d, 3H, J = 6.8 Hz, CH_3), 2.43 (sep, 1H, J = 6.8 Hz, CH), 4.83 (s, 1H, CH), 7.29 (s, 2H, NH_2), 7.32–7.80 (m, 5H, C_6H_5), 7.38 (t, 1H, J = 8.0 Hz, 4.0 Hz, pyridyl-H), 7.74 (dd, 1H, J = 8.0 Hz, 2 Hz, pyridyl-H), 8.49 (dd, 1H, J = 1.6 Hz, 4.8 Hz, pyridyl-H), 8.55 (d, 1H, J = 1.6 Hz, pyridyl-H). MS, m/z (%): 380 ($[M+Na]^+$, 50), 358 ($[M+H]^+$, 100). Anal. calcd. for $C_{21}H_{19}N_5O$ (357.41): C, 70.57; H, 5.36; N, 19.59. Found: C, 70.42; H, 5.29; N, 19.49.

Compound 5j. White crystals; mp 204–206 °C. IR (KBr, ν/cm^{-1}): 3373, 3175 (NH_2, br), 2182 (C≡N), 1658, 1594, 1515 (C=N, C=C). ^1H NMR (400 MHz, DMSO-d_6): δ = 0.91 (d, 3H, J = 7.2 Hz, CH_3), 1.06 (d, 3H, J = 7.2 Hz, CH_3), 2.21 (sep, 1H, J = 7.2 Hz, CH), 4.36 (s, 1H, J = 7.2 Hz, CH), 7.20 (s, 2H, NH_2), 7.33–798 (m, 12H, Ar-H). MS, m/z (%): 429 ($[M+Na]^+$, 50), 407 ($[M+H]^+$, 100). Anal. calcd. for $C_{26}H_{22}N_4O$ (406.49): C, 76.83; H, 5.46; N, 13.78. Found: C, 76.76; H, 5.39; N, 13.61.

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