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Diversity-oriented pyrazol-3-one synthesis based on hydrazinodipeptide-like units prepared via the Ugi reaction

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ABSTRACT

N-Cyanoacetyl-*N*′-trifluoroacetyl-*N*′-alkylhydrazines, prepared via hydrazino-Ugi reaction, provided different pyrazol-3-ones when exposed to mildly acidic and mildly basic conditions at 60 °C. These approaches offer a facile access to two different pyrazol-3-one-containing chemotypes in a diversity-oriented fashion, in only two chemical operations from simple precursors.

Reaction of hydrazine or a substituted hydrazine with 1,3-dicarbonyl compounds or synthetic equivalents thereof (β-oxoesters, β-oxonitriles, β-dialkylamino- or β-alkoxyvinyl ketones) is a classical way to pyrazole cores known as the Knorr pyrazole synthesis.[1] We have reported[2] on the preparation of hydrazinodipepetide-like units **1** via Ugi reaction involving trifluoroacetic acid as the acid component. The hydrazino-Ugi reaction initially yields hydrolytically prone trifluoroacetamides **2** which can be isolated and also converted in situ into **1** (Scheme 1). As compounds **1** can contain labile N^{β}-acyl groups (such as Ac or Boc), we thought it important to explore the potential of compounds **1** as synthons in the Knorr pyrazole synthesis, as such an approach may provide novel pyrazoles regiospecifically decorated with substituted acetamide side chains (to our knowledge, no reliable strategy to this end has been reported in the literature).

To our surprise, initial attempts to realize this approach were generally not very successful. First we tried to perform a stepwise condensation[3] of representative compound **1a** with cyanoacetone. While the enamine adduct **3** appeared to form (according to TLC analysis), addition of an equimolar amount of concd HCl led only to the formation of (DL)-*N*′-cyclohexyl-*N*-aminoleucineamide **4**. The latter could be condensed directly with aliphatic α-cyanoketones to give moderate yields of single regioisomers (as confirmed by HSQC spectra) of pyrazoles **5a,b** (Scheme 2). However, the range of suitable condensation partners for **4** appeared rather limited: for instance, we observed no reaction with bis-electrophiles **6**–**8** that we had previously condensed quite efficiently with hydrazine. The reasons for the inert character of **4** in these condensations are unclear. It may be rationalized by the steric bulk on one of the hydrazine nitrogen atoms (this should not preclude the compound from reacting at N^{β}). It is also possible that the secondary amide functionality deactivates N^{β} as well, via intramolecular hydrogen bonding (Fig. 1).

Prompted by these observations, we designed pyrazole precursors **9** containing both an electrophilic nitrile functionality and a reactive N^{α} atom (which we had shown previously to be a suitable reactive center for reductive amination[2] and a second Ugi reaction[4]). These precursors for intramolecular cyclization[5] (presumably, into 1-alkyl-5-amino-1,2-dihydro-3*H*-pyrazol-3-ones **10**) could be derived from the hydrazino-Ugi reaction products **11** by facile removal of the trifluoroacetyl group (Fig. 2). Such methodology was expected to allow exploration of the potential of post-condensation modifications of the hydrazino-Ugi core, an approach that had yielded numerous novel heterocyclic scaffolds when applied to classical Ugi products.[6]

However, when compounds **11** were prepared (notably, this further extends the scope of the hydrazino-Ugi reaction) and trifluoroacetyl group removal was attempted, the isolated products were the unexpected (and hitherto not described) 1-alkyl-3-oxo-5-(trifluoromethyl)-2,3-dihydro-1*H*-pyrazole-4-carbonitriles **12**. Under the typical conditions we had previously used[2] for CF_3CO group removal (10% K_2CO_3 in aqueous methanol, rt, 3 h) the conversion was slow (>3 days). Hence, the temperature was raised to

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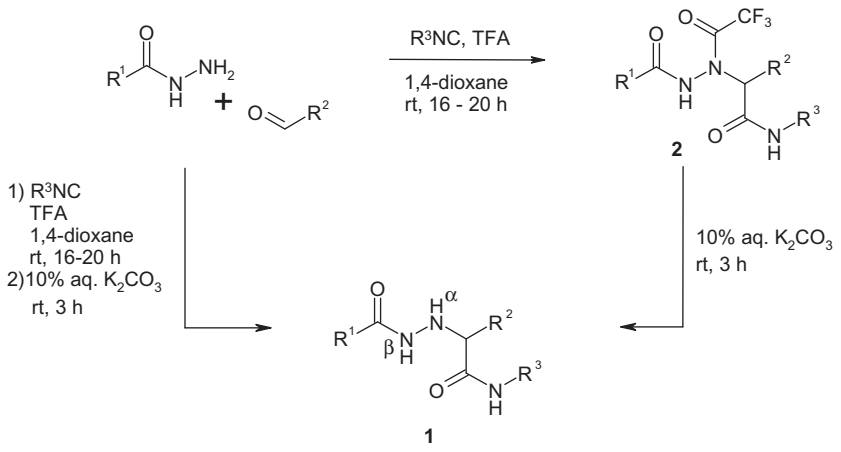
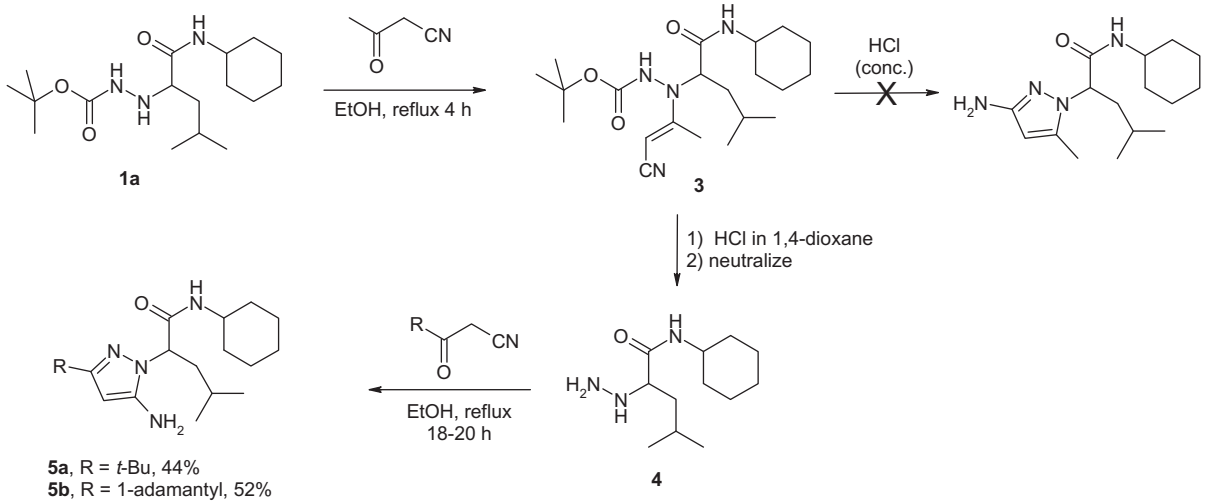


Scheme 1. The hydrazino-Ugi reaction and removal of a labile trifluoroacetyl group.[2]



Scheme 2. The use of **1a** as a synthon in the Knorr pyrazole synthesis.

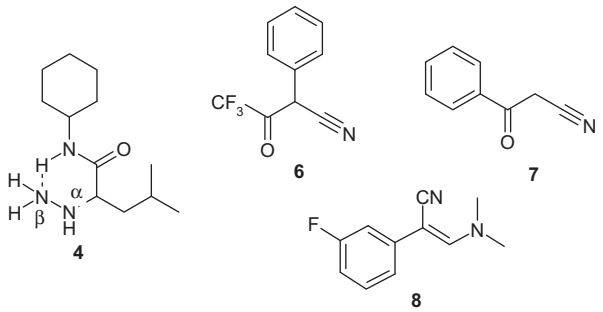


Figure 1. Suggested intramolecular hydrogen bonding in **4** and examples of unreactive bis-electrophile partners.

60 °C to increase the rate of reaction. In contrast, treatment with 0.5 M HCl in aqueous methanol at the same temperature led to the expected removal of the CF_3CO group and the clean formation of the pyrazol-3-ones **10** (Scheme 3). The isolated yields of both sets of pyrazol-3-ones **10** and **12** were good to excellent (Table 1). In some cases, products of analytical purity were isolated by simple filtration, whilst in other cases additional crystallization or column chromatographic purification was required. The structures of all the synthesized compounds were supported by ^1H and ^{13}C NMR spectra, LC–MS data, and elemental analyses.[7]

Mechanistically, the unexpected formation of **12** under basic conditions can be rationalized by deprotonation at the activated methylene group of **11** with subsequent cyclization onto the CF_3CO group

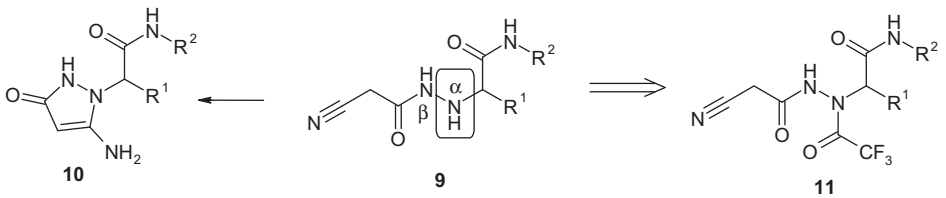
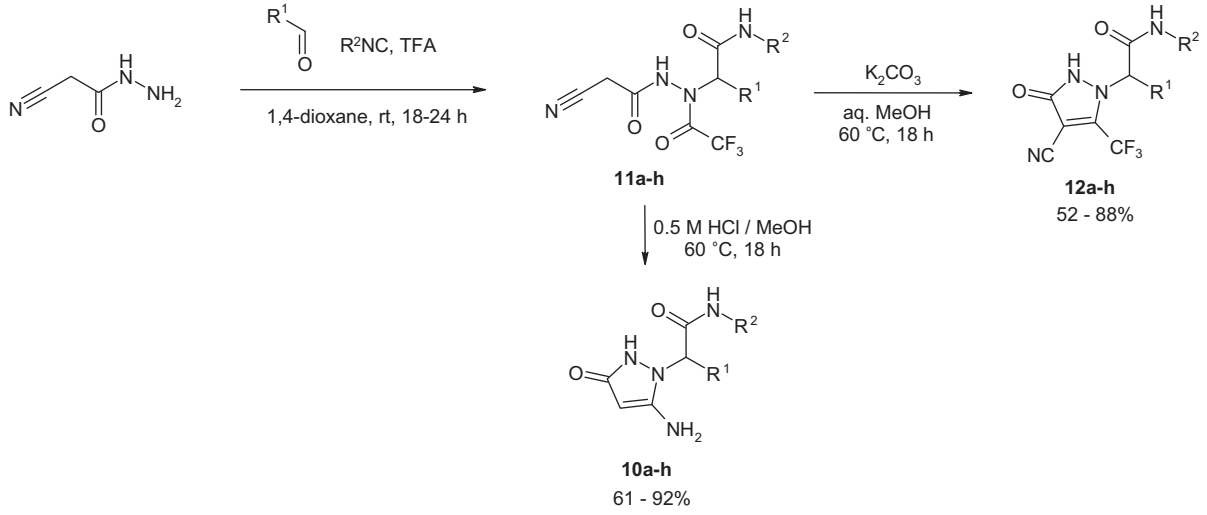


Figure 2. Cyanoacetyl hydrazine **9** designed as precursor for pyrazol-3-ones **10**.



Scheme 3. Hydrazino-Ugi reaction of cyanoacetyl hydrazine and further transformations of the products **11**.

Table 1
Compounds **10**–**12** prepared in this work

Entry	Product	R^1	R^2	Yield of **11** (%)	Yield of **10** (%)	Yield of **12** (%)
1	**10a**, **12a**	*i*-Bu	*t*-Bu	76[a]	52[a]	66[a]
2	**10b**, **12b**	*n*-Pr	*c*-Hex	82[a]	69[a]	74[b]
3	**10c**, **12c**	Et	*c*-Hept	64[a]	56[a]	77[b]
4	**10d**, **12d**	*t*-Bu	*i*-PrO$(CH_2)_3$	58[b]	88[a]	61[b]
5	**10e**, **12e**	*c*-Hex	4-Me$C_6H_4CH_2$	78[a]	59[b]	89[b]
6	**10f**, **12f**	Me	EtO$(CH_2)_3$	68[a]	65[b]	74[b]
7	**10g**, **12g**	*i*-Pr	4-F$C_6H_4CH_2$	47[b]	52[b]	69[b]
8	**10h**, **12h**	*c*-Hex	*t*-Bu	83[a]	86[a]	92[a]

[a] Yield of the analytically pure product isolated by filtration or by trituration with Et_2O.
[b] Yield after chromatography.

to give, after dehydration, the observed pyrazol-3-one **12**. Given the labile character of the trifluoroacetamide, the cyclization may be preceded by $N \rightarrow C$ migration of the CF_3CO group (Scheme 4).

The ability of **11** (or **9**) to undergo cyclization into the pyrazol-3-one should depend on the steric bulk, both at the activated methyl group of the cyanoacetyl side chain and at N^{α}. We discovered that the products **13a**,**b** (Fig. 3) synthesized via hydrazino-Ugi reaction from acetone and cyclohexanone as the carbonyl components, respectively, were completely inert toward such cyclization under acidic or basic treatment and only provided the respective de-trifluoroacetylated products. Moreover, we found that even a

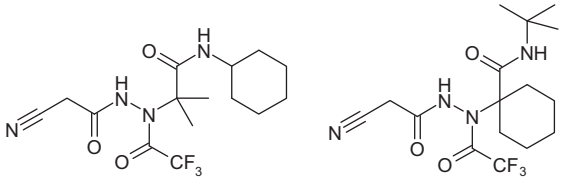
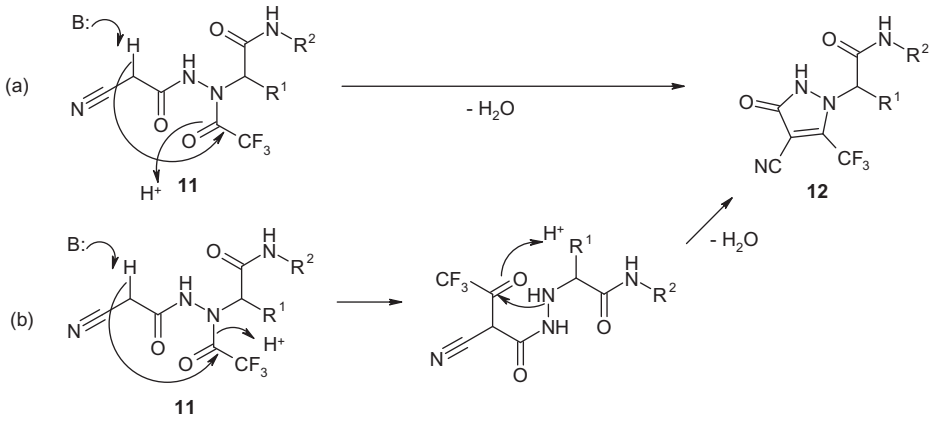
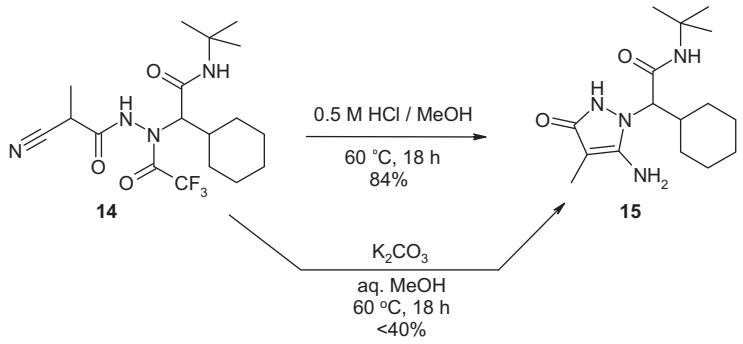


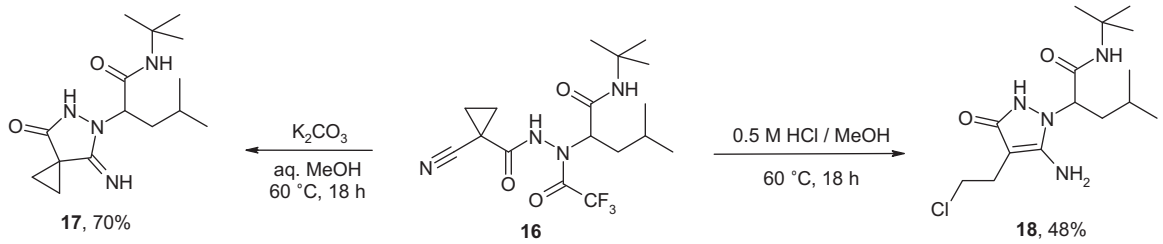
Figure 3. Bulky hydrazine derivatives that are inert toward cyclization into a pyrazol-3-one.



Scheme 4. Mechanistic rationale for the formation of the pyrazol-3-ones **12**.



Scheme 5. Cyclization of α-methyl derivative **14**.



Scheme 6. Cyclization of the cyclopropane derivative **16**.

small substituent such as a methyl group, when located at the methylene group of **10** (presumably, involved in cyclization leading to **12**), can affect the outcome of further cyclizations. Compound **14** (also prepared via hydrazino-Ugi reaction) provided an excellent yield of pyrazol-3-one **15** when treated with dilute acid (Scheme 5) and under basic conditions, the same compound yielded a complex mixture of products (including **15**), none of which contained a trifluoromethyl group.

An interesting result was obtained with the cyclopropane derivative **16**. Under basic conditions, it cyclized to give a good yield of 6-alkyl-7-imino-5,6-diazaspiro[2.4]heptan-4-one **17** (despite the even greater steric bulk at the nitrile function). Acidic treatment of **16** resulted in cycloprapane ring opening and isolation of 2-chloroethyl derivative **18** in fair yield (Scheme 6).

In summary, we have reported on a remarkable case of a switch in reactivity observed for the hydrazino-Ugi reaction products **11** under basic versus acidic conditions. This resulted in diversity-oriented access to two vastly different pyrazol-3-one-based chemotypes, one of which, **12**, has not been described in the literature. The absence, in these protocols, of regiochemical ambiguity with regard to alkylation of the pyrazol-3-one nucleus and the technical simplicity of its construction in two steps from available diverse reagents should make the described approach a useful method to prepare these novel peptidomimetic pyrazol-3-ones.

Synthesis of **11**; *typical procedure:* Cyanoacetylhydrazine (10 mmol) was dissolved in anhydrous MeOH (50 mL) and an aldehyde (11 mmol) was added. The mixture was stirred at rt for 3 h and the solvent was evaporated. The solid residue was triturated with Et_2O, filtered, and dissolved in dry 1,4-dioxane (20 mL). Isocyanide (12 mmol) and TFA (11 mmol) were added and the resulting mixture was stirred at rt overnight. It was then diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was triturated with Et_2O, filtered, and air-dried to provide analytically pure **11**, or further purified by column chromatography (SiO_2) using an appropriate gradient of MeOH in CH_2Cl_2 as eluent.

Synthesis of **10**; *typical procedure:* Compound **11** (0.5 mmol) was dissolved in MeOH (10 mL), treated with 0.5 M HCl (1 mL), and the resulting solution was stirred at 60 °C overnight. Upon cooling to rt, the MeOH was evaporated and the residue diluted with H_2O (20 mL), neutralized with solid Na_2CO_3, and the resulting precipitate was filtered and air-dried. Alternatively, the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extract dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2) using an appropriate gradient of MeOH in CH_2Cl_2 as eluent.

Synthesis of **12**; *typical procedure:* Compound **11** (0.5 mmol) was dissolved in MeOH (10 mL), treated 10% aq K_2CO_3 (5 mL), and the resulting solution was stirred at 60 °C overnight. Upon cooling to rt, the MeOH was evaporated and the residue diluted with H_2O (20 mL), neutralized with HCl, and the resulting precipitate was filtered and air-dried. Alternatively, the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2) using an appropriate gradient of MeOH in CH_2Cl_2 as eluent.

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7. *Characterization data for selected compounds*: Compound **10a**, white solid, mp = 128–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 1.22 (s, 9H), 1.30 (m, 1H), 1.56 (m, 1H), 1.91 (m, 1H), 4.42 (m, 1H), 4.56 (s, 1H), 5.47 (br s, 2H), 7.14 (br s, 1H), 9.35 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.4, 22.9, 24.3, 28.3, 49.9, 58.4, 74.3, 150.2, 161.8, 170.3. LC–MS (M+H$^+$) m/z = 269. Anal. Calcd for $C_{13}H_{24}N_4O_2$: C, 58.18; H, 9.01; N, 20.88. Found: C, 58.26; H, 8.92; N, 20.81. Compound **10d**, white solid, mp = 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.12 (d, J = 5.8 Hz, 6H), 1.62 (m, 2H), 3.32 (m, 2H), 3.44 (t, J = 6.6 Hz, 2H), 3.53 (m, 1H), 4.51 (s, 1H), 4.65 (s, 1H), 5.17 (br s, 2H), 8.11 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 27.2, 29.2, 36.5, 36.6, 65.1, 67.0, 69.9, 71.1, 152.5, 165.3, 168.5. LC–MS (M+H$^+$) m/z = 313. Anal. Calcd for $C_{15}H_{28}N_4O_3$: C, 57.67; H, 9.03; N, 17.93. Found: C, 57.60; H, 8.93; N, 17.88. Compound **12a**, white solid, mp = 143 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (d, J = 6.6 Hz, 6H), 1.25 (s, 9H), 1.36 (m, 1H), 1.66 (m, 1H), 2.28 (m, 1H), 4.92 (m, 1H), 7.86 (br s, 1H), 12.34 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.4, 23.0, 24.4, 28.1, 50.5, 62.3, 79.6, 110.7, 118.0 (q, J_{C-F} = 256.5 Hz), 133.3 (q, J_{C-F} = 38.2 Hz), 161.6, 167.0. LC–MS (M+H$^+$) m/z = 347. Anal. Calcd for $C_{15}H_{21}F_3N_4O_2$: C, 52.02; H, 6.11; N, 16.18. Found: C, 51.96; H, 6.04; N, 16.25. Compound **12d**, white solid, mp = 152–154 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03 (d, J = 5.9 Hz, 6H), 1.06 (s, 9H), 1.58 (m, 2H), 3.11 (m, 2H), 3.31 (t, J = 6.5 Hz, 2H), 3.46 (m, 1H), 4.43 (s, 1H), 7.85 (t, J = 5.4 Hz, 1H), 12.39 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.9, 27.3, 29.4, 35.7, 36.2, 64.7, 70.5, 70.7, 79.7, 110.6, 117.8 (q, J_{C-F} = 271.3 Hz), 134.3 (q, J_{C-F} = 38.2 Hz), 161.9, 164.7. LC–MS (M+H$^+$) m/z = 391. Anal. Calcd for $C_{17}H_{25}F_3N_4O_3$: C, 52.30; H, 6.45; N, 14.35. Found: C, 52.38; H, 6.46; N, 14.41.