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Synthesis of 4-imidazolin-2-ones from α-bromo ketimines

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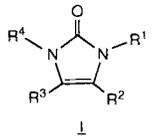
Abstract. A novel synthesis of 1,4-dialkyl-5-aryl-4-imidazolin-2-ones **3** has been achieved by reaction of α-bromo ketimines **2** with potassium cyanate in dimethylformamide. The structural assignment of the heterocycles was performed by spectrometric methods, comparison with a known compound and X-ray crystallographic analysis of the acetyl derivative **8**.

Introduction

4-Imidazolin-2-ones **1** (1,3-dihydro-2*H*-imidazol-2-ones) belong to a class of heterocyclic compounds which has been extensively studied. The major reason for the interest in these heterocycles originates from their multiple applications as agrochemicals and pharmaceuticals. A variety of 4-imidazolin-2-ones exhibits herbicidal[1,2] and bactericidal[3] activity, whereas some derivatives are useful as plant-growth regulators and as insect sterilants. A whole array of physiological activities in the pharmaceutical field is known for 4-imidazolin-2-ones, including uses as vasodilators[4], anticonvulsants[5], cardiotonics[6–8], antipyretics[9], analgesics[4,9], antidepressants[9], and antiinflammatory products[9]. A salient feature is that the 4-imidazolin-2-one nucleus is present in the alkaloid monospermine[10].



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Due to the plethora of applications of 4-imidazolin-2-ones in various fields, a lot of efforts have been devoted to synthetic entries into this class of heterocycles. Classical synthesis of 4-imidazolin-2-ones entail the condensation of α-amino ketones with isocyanates[1,11,12] and the cyclocondensation of (2-propynyl)ureas[9,13,14] or *N*-(2,2-dialkoxyalkyl)urea derivatives[1,15]. Related syntheses are the condensation of α-amino ketones with alkyl carbamates[4] or cyanogen bromide[16]. Urea or its derivatives have been condensed with several reagents, including α-halo ketones[17] or acyloins[18], to produce 4-imidazolin-2-ones. A recent paper is focussed on the synthesis of 4-imidazolin-2-ones from α-bromo ketones and potassium cyanate, carbon dioxide and ammonia[19]. 2,4-Imidazolidinediones have been shown to be useful substrates for synthesis of 4-imidazolin-2-ones by partial reduction[20] or alkyllithium addition[21] and subsequent dehydration. The dehydration of 4-hydroxy-2-imidazolidinones is closely related to the latter type of reactions[2,22]. Several rearrangements of heterocycles are also known to give rise to 4-imidazolin-2-ones.

In the present paper we describe a novel synthesis of 4-imidazolin-2-ones from readily available α-bromo ketimines. This simple pathway offers a new way to prepare the previously inaccessible 4-imidazolin-2-ones.

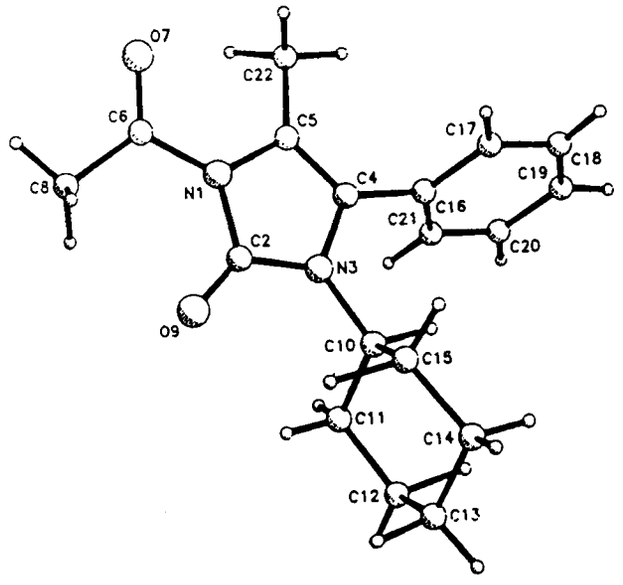

Figure 1. X-ray crystallographic picture of 1-acetyl-3-cyclohexyl-5-methyl-4-phenyl-4-imidazolin-2-one 8.

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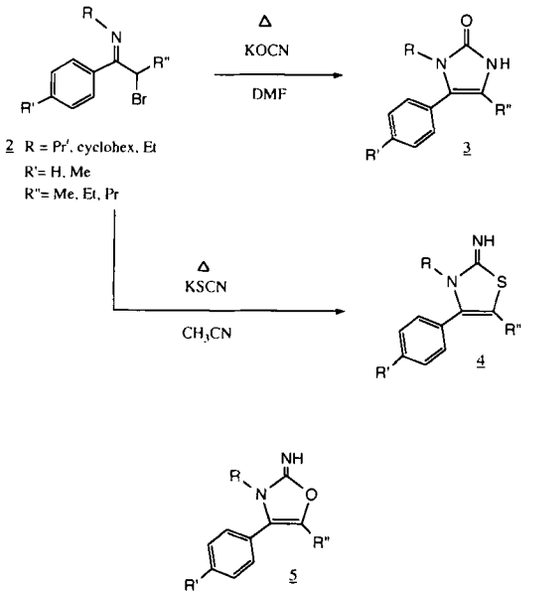
Results and discussion

Heating of N-(2-bromo-1-phenylpropylidene)isopropylamine (**2a**, R = Pr^i; R′ = H; R″ = Me) with potassium cyanate (1.5 molar equivalents) in acetonitrile revealed almost no disappearance of starting material after 45 min. Heating the reactants for an extended period (44 h) afforded a reaction mixture containing 50% of a major reaction product and still 40% of unreacted α-bromo ketimine **2a**. Complete conversion of the starting material could be accomplished after five days of reflux under the given conditions. From this reaction mixture, 1-isopropyl-4-methyl-5-phenyl-4-imidazolin-2-one (**3a**) was isolated in 31% yield. The structural elucidation of this heterocyclic compound will be discussed below. The reaction time could be drastically reduced by performing the reaction of α-bromo ketimines **2** with potassium cyanate in dimethylformamide (DMF) at 120°C for 1–2½ h, affording 5-aryl-1,4-dialkyl-4-imidazolin-2-ones **3** in 22–70% yield (Scheme 1). All heterocycles **3** were isolated as white solids except compound **3e** which was obtained as a viscous oil (Table I).



Scheme 1.

The structural elucidation of the heterocycles obtained from the reaction of α-bromo ketimines **2** with potassium cyanate met difficulties. The mass spectrum revealed a molecular ion in all cases, which was indicative of a structure in which the starting material had been dehydrobrominated and in which a cyanate moiety had been built into the molecule. Owing to the ambident character of the cyanate ion, two heterocyclic structures might be viewed as candidates for the final structure, *i.e.* 4-imidazolin-2-ones **3** and 2-imino-4-oxazolines **5**. Based on

Table I Synthesis of 4-Imidazolin-2-ones 3 and 6

Starting material	R	R′	R″	R‴	Reaction conditions	Yield (%)	M.p. (°C)	IR (KBr) (cm^{-1})	Mass spectrum (70 eV) [a] [m/z (%)]
2a	Pr^i	H	Me	H	3 equiv. KOCN/MeCN/ reflux 115 h	31 (**3a**)	175	1670 (s)	216 (M$^+$, 10); 105(100); 104 (45); 77(50); 44(45); 43(35)
2a	Pr^i	H	Me	H	4 equiv. KOCN/DMF/ 120°C/2½ h	22 (**3a**)	175	–	–
2b	Pr^i	H	Et	H	1.5 equiv. KOCN/DMF/ 120°C/2 h	35 (**3b**)	126	1670 (s)	230 (M$^+$, 70); 188(72); 173 (100); 104(26); 49(35); 40(64)
2c	cyclohex	H	Me	H	1.5 equiv. KOCN/DMF/ 120°C/ 1 h	43 (**3c**)	231 (decomp.)	1670 (s)	256 (M$^+$, 23); 174(100); 104 (11); 43(20); 41(11); 40(12)
2d	Pr^i	Me	Me	H	1.5 equiv. KOCN/DMF/ 120°C/2 h	70 (**3d**)	217	1670 (s)	230 (M$^+$, 43); 188(100); 118 (19); 43(31); 42(16); 41(10)
2e	Pr^i	H	Pr	H	1.5 equiv. KOCN/DMF/ 120°C/2 h	55 (**3e**)	– [b]	1650–1700 (s,br)	244 (M$^+$, 48); 202(24); 173 (100); 130(18); 103(16); 44(60)
2f	Et	H	Me	H	1.5 equiv. KOCN/DMF/ 120°C/2½ h	50 (**3f**)	147 [c]	1675 (s)	202 (M$^+$, 100); 174(41); 173 (29); 104(24); 77(24); 43(31) [d]
2g	cyclohex	H	Me	Ac	excess Ac_2O/ reflux/3 h	92 (**6**)	118	1715 (s) 1650–1700 (m,br)	298 (M$^+$, 8); 256(45); 174(100); 130(8); 104(12); 77(8); 55(20)

[a] The molecular ion (M$^+$) and the five most abundant fragments are given. [b] Oil. [c] Lit. m.p. 144–146°C[37]. [d] Identical in all details with the same compound obtained from an alternative synthesis[37].

Table II Selected ^{1}H-NMR and ^{13}C-NMR (δ, $CDCl_3$) data of 4-imidazolin-2-ones 3 and 6.

Compd.	^{1}H NMR				^{13}C NMR			
	δ (R)	δ (R″)	δ (R‴)	δ (R″)	=C–R″ (s)	=C–N (s)	C_α(R)	C=O (s)
3a	1.40, 6 H, d, J 6.5 Hz, Me_2; 4.03 1 H, septet, J 6.5 Hz, CH	2.00, s	10.4, s, br	9.88, q	115.08	119.97	46.18, d	154.39
3b	1.41, 6 H, d; J 6.5 Hz, Me_2; 4.00, 1 H, septet, J 6.5 Hz, CH	2.34, q, J 7 Hz; 1.16, t, J 7 Hz	11.3, s, br	17.94, t 13.63, q	119.16	121.14	46.09, d	154.73
3c	0.9–2.4, 10 H, m, $(CH_2)_5$; 3.6, 1 H, m, CH	2.02, s	10.5, s, br	10.01, q	115.01	120.17	54.37, d	154.36
3d	1.40, 6 H, d, J 7 Hz, Me_2; 4.05, 1 H, septet, J 7 Hz, CH	1.98, s	10.5, s, br	9.85, q	114.76	119.98	46.14, d	154.29
3e	1.40, 6 H, d, J 7 Hz, Me_2	2.30, t, J 7.5 Hz; 1.5, m; 0.9, t	10.5, s, br	26.41, t; 22.06, t; 13.59, q	119.49	120.04	46.15, d	154.47
3f	1.06, 3 H, t, J 6.5 Hz, Me; 3.76, 2 H, q, J 6.5 Hz, CH_2	2.10, s	11.2, s, br	9.82, q	115.28	119.79	36.23, t	154.41
6	0.9–2.4, 10 H, m, $(CH_2)_5$; 3.1–3.8, 1 H, m, NCH	2.16, s	2.70, s	12.56, q	115.50	123.89	54.90, d	151.82

the fact that α-bromo ketimines **2** react with potassium thiocyanate to afford 2-imino-4-thiazolines **4**, exclusively[23], and analogous arrangement of the ambident nucleophilic cyanate in the final heterocycles would yield 2-imino-4-oxazolines **5**.

However, the strong IR absorption (solid state) at 1670 cm^{-1} pointed in favor of carbonyl-containing compounds, *i.e.* 4-imidazolin-2-ones (**3**). ^{1}H-NMR and ^{13}C-NMR data (Table II) do not allow differentiation between structural isomers **3** and **5**.

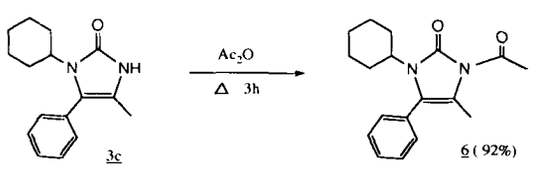
Out of the series of compounds **3** prepared (Table I), one derivative was known in the literature[37], namely 1-ethyl-4-methyl-5-phenyl-4-imidazolin-2-one (**3f**, R = Et; R′ = H; R″ = Me). The latter compound was obtained from the reaction of 2-amino-1-phenyl-1-propanone (as hydrochloride) with ethyl isocyanate and subsequent thermal dehydration of the resulting 4-hydroxyimidazolidin-2-one[11]. That such syntheses of 4-imidazolin-2-ones (**3f**, R = Et, R′ = H, R″ = Me) are not easily performed is illustrated by the low yield (14%) of 3-ethyl-5-methyl-4-phenyl-4-imidazolin-2-one obtained from 2-amino-1-phenyl-1-propanone. Our compound **3f**, obtained from α-bromo ketimine **2f** and potassium cyanate, had a melting point (147°C) comparable to that of the known compound (144–146°C)[11]. In addition, the ^{1}H-NMR spectra data[11] and the mass-spectral fragmentations[11] of both compounds were identical.

The mass spectra of a variety of 4-imidazolin-2-ones were studied extensively, allowing differentiations of positional isomers[11]. Isomeric 4-imidazolin-2-ones, substituted with alkyl and phenyl substituents, gave almost identical mass spectra but the positional isomers could easily be distinguished by different fragmentation patterns in both metastable- and collisional-activation spectra of the molecular ions. Reviewing the mass spectrum of the heterocycle **3f**, prepared from α-bromo ketimine **2f**, it was noticed that the expected diagnostic ion Ph–C≡N$^+$–Et was not present, but that the non-diagnostic Ph–C≡N$^+$H was abundantly present (24%). This observation should be kept in mind when analyses of mass spectra of isomeric 4-imidazolin-2-ones are performed.

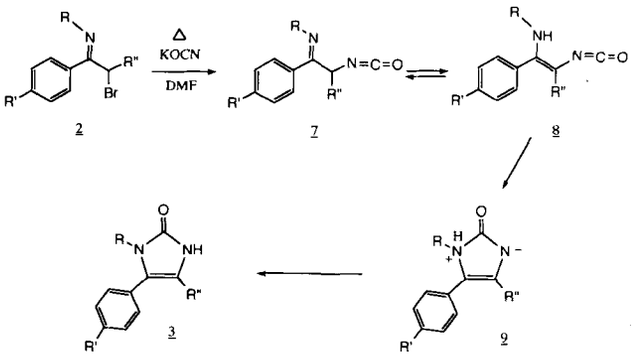
Obtaining crystals of heterocycles **3**, suitable for an X-ray crystallographic analysis, proved to be difficult and, therefore, the α-acetyl derivative **6** was prepared from **2c** (Scheme 2).

Heating of 1-cyclohexyl-4-methyl-5-phenyl-4-imidazolin-2-one (**3c**) with excess acetic anhydride for three hours resulted in a 92% yield of 1-acetyl-3-cyclohexyl-5-methyl-4-phenyl-4-imidazolin-2-one (**6**), which afforded parallelepiped single crystals from ether. The X-ray crystallographic analysis unambiguously proved the 4-imidazoline-2-one structure. The X-ray crystallographic analysis of compound **6** is depicted in Figure 1.

The structure of the 4-imidazolin-2-ones being solved, attention can be payed to the mechanism of the reaction leading to these heterocycles. The mechanism is interpreted in terms of a nucleophilic substitution of the heteroallylic bromide in **2** by the N terminus of the ambident cyanate anion (Scheme 3). Tautomerism into enamine **8**, produces a nucleophilic nitrogen, suitable for intramolecular nucleophilic addition across the heterocumulene. The cyclization of intermediate **8** might also involve a 6-π electrocyclic reaction. An alternative route involving initial addition of the nitrogen of the enamine derived from α-bromo ketimine **2** across the heterocumulene and subsequent intramolecular nucleophilic substitution by the nitrogen of the adduct, cannot be excluded. Still, the duality in the reactivity of α-bromo ketimines towards thiocyanate or cyanate ion remains, although it should be kept in mind that the reaction media for both reactions differ markedly (acetonitrile with respect to dimethylformamide). The former reaction is run at reflux in acetonitrile while the latter is performed at 110°C. The much higher temperature at which the reaction leading to 4-imidazolin-2-ones is executed allows speculation on the initial formation of 2-imino-4-oxazolines **5** which might rearrange into the final 4-imidazoline-2-ones **3**. This transformation is known in the literature under thermal conditions[26,27].



Scheme 2.



Scheme 3.

Experimental

Infrared spectra were recorded with a Perkin Elmer model 1310 spectrophotometer. ^{1}H-NMR spectra were measured with a Varian T-60 NMR spectrometer while ^{13}C-NMR spectra were recorded with a Varian FT-80 NMR spectrometer. Mass spectra were obtained with a Varian MAT 112 mass spectrometer using the direct inlet system (70 eV). Melting points were recorded with a Kofler hotstage and are uncorrected. All α-bromo ketimines **2** were synthesized according to our previously published general method for the preparation of α-halo imines[28].

Synthesis of 1,4-dialkyl-5-aryl-4-imidazolin-2-ones 3 (Table I)

The synthesis of 1-cyclohexyl-4-methyl-5-phenyl-4-imidazolin-2-one (**3c**) (R = cyclohexyl; R′ = H; R″ = Me) is representative of all syntheses of the heterocycles **3**. A solution of 2.94 g (0.01 mol) of N-(2-bromo-1-phenylpropylidene)cyclohexylamine (**2c**) in 20 ml of dimethylformamide was treated with 1.21 g (0.015 mol) of potassium cyanate. The mixture was stirred at 120°C (oil bath) for 1h, after which the reaction mixture was poured into 200 ml of water. Extraction was performed with ether (3–5 times) until all the white precipitate present had been taken up by the organic solvent. Drying of the combined extracts and evaporation of the solvent afforded a white precipitate, which was dissolved under reflux in the minimum amount of dry diethyl ether. Crystallization in diethyl ether at −20°C gave a white powder, consisting of pure **3c** (1.1 g, 43%), m.p. 231°C (decomp.).

Elemental analyses of compounds **3**. **3a** calcd.: C 72.19, H 7.46, N 12.95; found: C 72.30, H 7.59, N 12.79%. **3b** calcd. C 73.01, H 7.88, N 12.16; found: C 73.12, H 7.95, N 12.08. **3c** calcd. C 74.97, H 7.86, N 10.93; found: C 74.79, H. 7.93, N 10.98%. **3d** calcd.: N 12.16; found N 12.22%.

Synthesis and X-ray crystallographic parameters of 1-acetyl-3-cyclohexyl-5-methyl-4-phenyl-4-imidazolin-2-one (6) (Table I)

A solution of 128 mg (0.5 mmol) of 1-cyclohexyl-4-methyl-5-phenyl-2-imidazolin-2-one (**3c**) in 3 ml of acetic anhydride was refluxed for 3

Table III. Atomic coordinates ($\times 10^4$) and equivalent temperature factors ($Å^2$).

Atom	x/a	y/b	z/c	B_{eq} [a]
N1	3973(2)	3717(2)	6515(1)	4.15(4)
C2	4442(3)	3011(3)	5901(2)	4.36(5)
N3	5729(2)	3392(3)	5960(1)	4.27(4)
C4	6065(3)	4324(3)	6582(1)	3.99(5)
C5	5013(3)	4525(3)	6931(1)	4.05(5)
C6	2694(3)	3573(4)	6710(2)	4.94(6)
O7	2508(2)	3882(4)	7337(1)	7.17(6)
C8	1619(4)	3090(5)	6108(3)	6.49(8)
O9	3825(2)	2204(3)	5436(1)	5.96(5)
C10	6676(3)	2783(4)	5490(2)	5.05(6)
C11	6374(4)	3181(4)	4684(2)	6.29(8)
C12	7404(5)	2635(5)	4228(2)	7.28(9)
C13	7796(5)	1097(5)	4373(2)	7.15(9)
C14	8099(4)	722(5)	5202(2)	5.87(7)
C15	6996(4)	1217(5)	5633(2)	6.80(8)
C16	7391(3)	5012(3)	6750(2)	4.30(5)
C17	8252(3)	4570(4)	7371(2)	5.63(7)
C18	9492(4)	5220(6)	7505(2)	6.93(8)
C19	9858(4)	6279(5)	7035(3)	6.95(9)
C20	8998(4)	6716(5)	6420(3)	6.66(8)
C21	7767(3)	6097(4)	6278(2)	5.56(6)
C22	4875(4)	5524(4)	7575(2)	5.55(7)

[a] $B_{eq} = \frac{8}{3} \cdot \pi^2 \Sigma_i \Sigma_j (\sigma_j \cdot U_{ij} \cdot a_i^* \cdot a_j^* \cdot a_i \cdot a_j)$

Table IV Bond distances

Bond	Distance (Å)	Bond	Distance (Å)
C2–N1	1.414(3)	C5–N1	1.416(3)
C6–N1	1.412(3)	N3–C2	1.356(3)
O9–C2	1.216(3)	C4–N3	1.400(3)
C10–N3	1.480(3)	C5–C4	1.334(3)
C16–C4	1.489(4)	C22–C5	1.487(4)
O7–C6	1.198(4)	C8–C6	1.494(5)
C11–C10	1.476(5)	C15–C10	1.470(5)
C12–C11	1.508(5)	C13–C12	1.462(5)
C14–C13	1.509(5)	C15–C14	1.525(5)
C17–C16	1.378(4)	C21–C16	1.385(4)
C18–C17	1.392(5)	C19–C18	1.364(6)
C20–C19	1.368(6)	C21–C20	1.374(5)

Table V Bond angles

Bond	Angle (°)	Bond	Angle (°)
C5–N1–C2	109.1(2)	C6–N1–C2	125.5(2)
C6–N1–C5	125.3(2)	N3–C2–N1	105.1(2)
O9–C2–N1	127.0(3)	O9–C2–N3	127.9(3)
C4–N3–C2	110.1(2)	C10–N3–C2	125.0(2)
C10–N3–C4	124.6(2)	C5–C4–N3	109.2(2)
C16–C4–N3	121.9(2)	C16–C4–C5	128.8(2)
C4–C5–N1	106.6(2)	C22–C5–N1	125.0(2)
C22–C5–C4	128.1(3)	O7–C6–N1	119.1(3)
C8–C6–N1	117.9(3)	C8–C6–O7	122.9(3)
C11–C10–N3	113.6(3)	C15–C10–N3	114.1(3)
C15–C10–C11	114.6(3)	C12–C11–C10	112.4(3)
C13–C12–C11	114.4(3)	C14–C13–C12	113.7(3)
C15–C14–C13	111.5(3)	C14–C15–C10	111.0(3)
C17–C16–C4	120.4(3)	C21–C16–C4	119.9(3)
C21–C16–C17	119.6(3)	C18–C17–C16	118.9(4)
C19–C18–C17	121.0(4)	C20–C19–C18	119.8(4)
C21–C20–C19	120.2(4)	C20–C21–C16	120.4(4)

h. Evaporation of acetic anhydride *in vacuo* gave a solid residue, which was recrystallized from the minimum amount of dry ether at −20°C affording 137 mg (92%) of colorless "bricks", m.p. 118°C. Anal. calcd. N 9.39; found: N 9.46%.

The principal X-ray crystallographic parameters of compound **6** are as follows: $M_r = 298.39$, monoclinic, $P2_1/n$, $a = 10.273(2)$, $b = 9.052(2)$, $c = 17.894(4)$ Å, $\beta = 98.13(2)°$, $V = 1647.3(6)$ Å^3, $Z = 4$, $D_x = 1.20$ g/cm^3, CuKα, $\lambda = 1.5418$ Å, $\mu = 6.36$ cm^{-1}, $F(000) = 640$, $T = 291$K, $R = 0.071$ for 2348 observed reflections. Lattice parameters were refined using 19 reflections in the range $5° \leq 2\theta \leq 30°$. The structure was solved by SHELX 86[24]. Atomic-scattering factors were obtained from the International Tables for X-ray Crystallography Vol. IV[25]. Table III shows the atomic coordinates and equivalent temperature factors, while Table II reveals the bond distances. The bond angles are represented in Table V and the torsion angles are gathered in Table VI.

Table VI Torsion angles ($\sigma = 1$)

Bond	Angle (°)	Bond	Angle (°)
C5–N1–C2–N3	0	N3–C4–C5–N1	0
C5–N1–C2–O9	178	N3–C4–C5–C22	−174
C6–N1–C2–N3	−176	C16–C4–C5–N1	175
C6–N1–C2–O9	2	C16–C4–C5–C22	1
C2–N1–C5–C4	0	N3–C4–C16–C17	−110
C2–N1–C5–C22	174	N3–C4–C16–C21	69
C6–N1–C5–C4	177	C5–C4–C16–C17	74
C6–N1–C5–C22	−9	C5–C4–C16–C21	−106
C2–N1–C6–O7	160	N3–C10–C11–C12	176
C2–N1–C6–C8	−22	C15–C10–C11–C12	−50
C5–N1–C6–O7	−16	N3–C10–C15–C14	−173
C5–N1–C6–C8	162	C11–C10–C15–C14	54
N1–C2–N3–C4	−1	C10–C11–C12–C13	47
N1–C2–N3–C10	173	C11–C12–C13–C14	−48
O9–C2–N3–C4	−179	C2–C13–C14–C15	50
O9–C2–N3–C10	−5	C13–C14–C15–C10	−52
C2–N3–C4–C5	1	C4–C16–C17–C18	179
C2–N3–C4–C16	−175	C21–C16–C17–C18	0
C10–N3–C4–C5	−173	C4–C16–C21–C20	−179
C10–N3–C4–C16	11	C17–C16–C21–C20	1
C2–N3–C10–C11	65	C16–C17–C18–C19	0
C2–N3–C10–C15	−68	C17–C18–C19–C20	0
C4–N3–C10–C11	−122	C18–C19–C20–C21	0
C4–N3–C10–C15	104	C19–C20–C21–C16	−1

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