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# Stereoselective intramolecular cycloadditions of homochiral nitrilimines: synthesis of enantiopure (6*S*)-substituted-2,3,3a,4,5,6-hexahydro-furo[3,4-*c*]pyrazoles

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**Abstract**—Starting from (*S*)-ethyl lactate and (*S*)-ethyl mandelate the homochiral hydrazonoyl chlorides **4b–d** have been synthesised. Their base treatment promoted the in situ generation of the corresponding nitrilimines **5b–d**, which gave the enantiopure title compounds with good overall yields and diastereoselectivities.


## 1. Introduction

Stereoselective 1,3-dipolar cycloadditions represents one of the most productive fields of modern synthetic organic chemistry.[1] As a result, the behaviour of a large array of 1,3-dipolar functionalities have been exploited in the construction of a number of enantiopure five-membered heterocycles.[2] However, despite the utility of enantiopure 4,5-dihydropyrazole derivatives in organic synthesis[3] and some interesting applications of the related products,[4] the stereoselective cycloadditions of nitrilimines have scarcely been investigated. The first case of asymmetric induction in intramolecular nitrilimine cycloaddition was reported by our laboratory,[5] and up until now, this approach to fused bi- or tricyclic 4,5-dihydropyrazoles has received little attention.[6] This lack of experimental data led us to investigate in more detail the behaviour in terms of stereoselectivity of nitrilimines **5b–d** in which the stereocentre is placed inside the tether joining the reactive groups. Furthermore, having recognised that the synthesis of enantiopure molecules from simple starting materials is a valuable target,[7] we developed the inexpensive, commercially available (*S*)-ethyl lactate and (*S*)-ethyl mandelate as suitable starting chiral units.

## 2. Results and discussion

Our synthetic sequence starts from the known ethyl (2*S*)-substituted-2-allyloxyacetates **1a–d**[8] as the chiral building blocks. Their basic hydrolysis followed by treatment with thionyl chloride gave the corresponding (2*S*)-substituted-2-allyloxyacetyl chlorides **2a–d**, which were used as crude materials without isolation. Acyl hydrazide intermediates **3a–d** were obtained pure from the latter by treatment with phenylhydrazine. Hydrazonoyl chlorides **4a–d** were synthesised from acyl hydrazides **3a–d** via treatment with triphenylphosphine and carbon tetrachloride according to the method originally proposed by Wolkoff[9] (Scheme 1). The in situ generation of labile intermediates **5a–d** was accomplished by refluxing the corresponding hydrazonoyl chlorides **4a–d** with an excess of triethylamine (5 equiv) in dry toluene, thus following the classic Huisgen's nitrilimine cycloaddition protocol.[10] Reaction times, overall product yields and diastereoisomeric ratios are summarised in Table 1. In the case of unsubstituted **5a**, simple crystallisation of the crude gave the racemic mixture **6a** and **7a** in analytically pure form with 96% overall yield. Spectral data of these cycloadducts are fully consistent with those reported for similar furo[3,4-*c*]pyrazoles.[11]

The diastereoisomeric cycloadducts **6b–d** and **7b–d** were obtained chemically and enantiomerically pure through silica gel column chromatography. Their isolated yields ranged from fair to good, with some tarry material being formed. The absolute configurations of the newly

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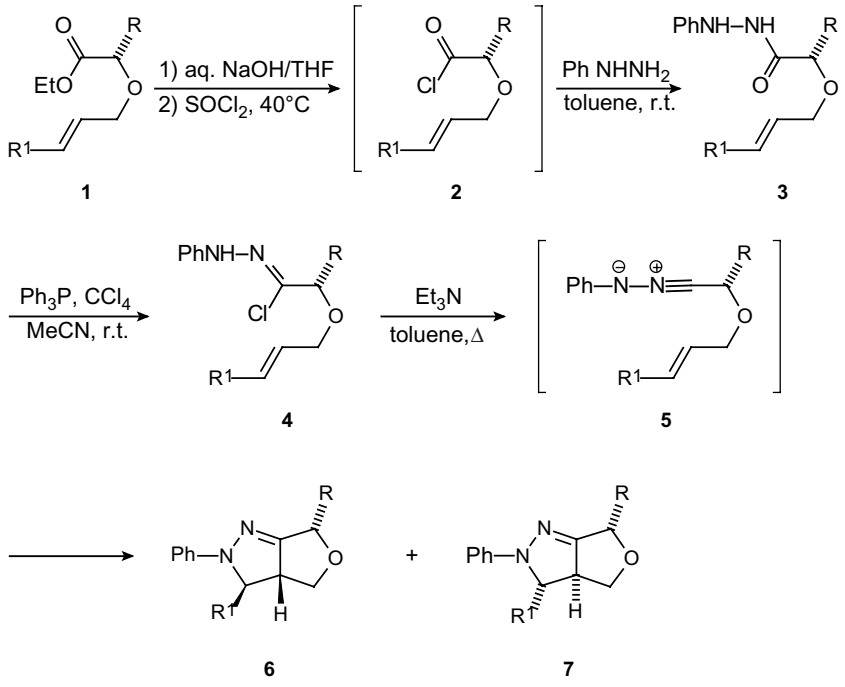



| Entry | a | b | c | d |
|---|---|---|---|---|
| R | H | Me | Me | Ph |
| $R^1$ | H | H | Me | H |

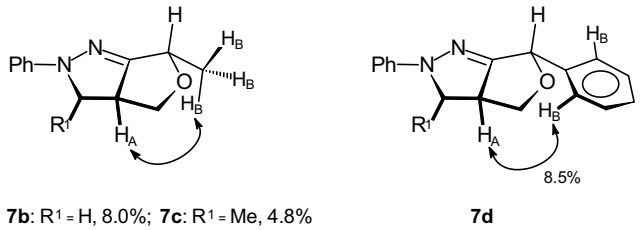
**Scheme 1.**

**Table 1.** Intramolecular cycloadditions of nitrilimines **5**[a]

| Entry | R | $R^1$ | Time (h) | **6** and **7** (%)[b] | **6**/**7**[c] |
|---|---|---|---|---|---|
| **a** | H | H | 3 | 96 | 50:50 |
| **b** | Me | H | 4 | 74 | 86:14 |
| **c** | Me | Me | 8 | 65 | 70:30 |
| **d** | Ph | H | 5 | 39 | 100:0 |

[a] In refluxing toluene.
[b] Overall yields.
[c] Determined from $^1$H NMR analysis of reaction crudes.

formed stereocentres of minor **7b–d** were determined unambiguously by the mutual NOE enhancements reported in Figure 1. It is apparent that the observed NOE effects can be operative only in the case of the depicted stereochemical arrangement. Furthermore, AM1[12] calculated distances between $H_A$ and the average position of $H_B$ were 2.79 Å for **7b**, 2.81 Å for **7c**, 2.73 Å for **7d**,[13] thus justifying the observed mutual NOE enhancements. As far as diastereoselection is concerned, it can be inferred that: (i) the relative configurations of the newly formed stereocentres of cycloadducts **6c** and **7c** is *anti* as a consequence of the concerted cycloaddition mechanism, and (ii) the ratio **6b–d**/**7b–d** encompasses the range between 70:30 and 100:0 depending upon the size and shape of R and $R^1$. These results may account for the proposed transition states **A** and **B** (Fig. 2). Due to the inner disposition of R, transition state **B** should be the less stable one giving minor **7b–d**; the intervention of such a transition state is made impervious in the case of the bulky phenyl pendant. Hence, the preferred formation of major **6b–d** finds rationalisation.




**7b**: $R^1$ = H, 8.0%; **7c**: $R^1$ = Me, 4.8%

**Figure 1.** NOE enhancements for cycloadducts **6** and **7**.

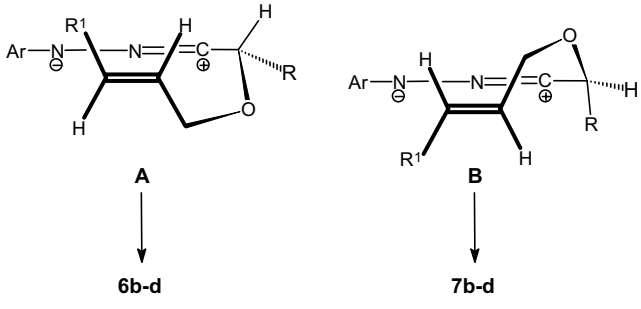



**Figure 2.** Proposed transition states for the formation of cycloadducts **6b–d** and **7b–d**.

## 3. Conclusion

In conclusion, the favourable entropic effects, which work in the formation of the furo[3,4-*c*]pyrazole skeleton, makes the intramolecular cycloaddition of nitrilimines **5a–d** very efficient and hence valuable on a preparative scale.

## 4. Experimental section

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. $^1$H NMR (300 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. NOE experiments were performed by setting the following parameters: relaxation delay (d1) 2 s, irradiation power (dl2) 74 dB and total irradiation time (for each signal) 1.8 s. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at the sodium D-line at 25 °C.

### 4.1. Synthesis of ethyl (2*S*)-but-2-enyloxylactate 1c

$Ag_2O$ (2.32 g, 10.0 mmol) was added portionwise, under vigorous stirring, to a solution of ethyl (2*S*)-lactate (1.18 g, 10.0 mmol) and 1-bromobut-2-ene (1.69 g, 12.5 mmol) in anhydrous diethyl ether (25 mL) at room temperature. The mixture was refluxed for 3 h, then cooled and filtered over Celite. The organic layer was dried over sodium sulfate, the solvent evaporated and the residue distilled in vacuo giving **1c** (1.53 g, 89%); pale yellow oil. $[\alpha]_D^{25} = -21.8$ (*c* 0.16, $CHCl_3$); IR (neat) 1745 cm$^{-1}$; $^1$H NMR $\delta$ 1.35 (3H, t, *J* 4.1), 1.45 (3H, t, *J* 6.4), 1.70 (3H, d, *J* 7.1), 4.16 (2H, q, *J* 6.4), 5.08 (2H, d, *J* 5.2), 5.25–5.90 (3H, m). MS *m/z*: 172 ($M^+$). Anal. Calcd for $C_9H_{16}O_3$: C, 62.80; H, 9.36. Found: C, 62.85; H, 9.40.

### 4.2. Synthesis of acyl hydrazides 3

A solution of the appropriate 2-allyloxyacetate **1** (7.5 mmol) in tetrahydrofuran (75 mL) was treated with 2 M aqueous sodium hydroxide (75 mL) and stirred at room temperature for 3 h. Aqueous 6 M hydrochloric acid was added until pH 1 and the mixture extracted twice with ethyl acetate (2 × 100 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. Thionyl chloride (0.89 g, 7.5 mmol) was added dropwise to the oily residue under vigorous stirring, and the mixture warmed to 40 °C for 2 h. The excess of thionyl chloride was removed by in vacuo distillation giving crude 2-allyloxyacetyl chlorides **2** as dark brown oils. Freshly distilled triethylamine (1.52 g, 15.0 mmol) was added dropwise to a solution of **2** in dry toluene (25 mL) at room temperature. After 15 min phenylhydrazine (0.81 g, 7.5 mmol) was added and the mixture stirred at room temperature for 4 h. Water (50 mL) was added to reaction mixture, the organic layer separated, dried over sodium sulfate and evaporated under reduced pressure. The dark red residue was chromatographed on a silica gel column with ethyl acetate–hexane 4:1 giving acyl hydrazides **3**.

**4.2.1. Compound 3a.** 0.73 g, 47%. White powder; mp 70 °C (from diisopropyl ether); IR (nujol) 3310, 3240, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.08 (2H, d, *J* 4.6), 4.12 (2H, s), 5.21–5.93 (3H, m), 6.08 (1H, br d, *J* 4.2), 6.8–7.3 (5H, m), 8.22 (1H, br s); MS *m/z* 206 ($M^+$). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.10; H, 6.87; N, 13.62.

**4.2.2. Compound 3b.** 0.99 g, 60%. White powder; mp 61 °C (from diisopropyl ether); $[\alpha]_D^{25} = -16.6$ (*c* 0.16, $CHCl_3$); IR (nujol) 3310, 3230, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.48 (3H, d, *J* 6.5), 4.10 (1H, q, *J* 6.5), 4.12–4.20 (2H, m), 5.12–5.90 (3H, m), 6.07 (1H, br d, *J* 4.3), 6.8–7.3 (5H, m), 8.30 (1H, br s); MS *m/z* 220 ($M^+$). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.40; H, 7.36; N, 12.77.

**4.2.3. Compound 3c.** 0.76 g, 43%. White powder; mp 58 °C (from diisopropyl ether); $[\alpha]_D^{25} = -18.3$ (*c* 0.75, $CHCl_3$); IR (nujol) 3300, 3225, 1660 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.02 (3H, d, *J* 6.4), 1.74 (3H, d, *J* 5.0), 4.08 (2H, d, *J* 4.7), 4.16 (1H, q, *J* 6.4), 5.15–5.85 (2H, m), 6.05 (1H, br d, *J* 4.2), 6.8–7.3 (5H, m), 8.25 (1H, br s); MS *m/z* 234 ($M^+$). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 61.52; H, 7.74; N, 11.96. Found: C, 61.55; H, 7.76; N, 12.03.

**4.2.4. Compound 3d.** 0.70 g, 33%. White powder; mp 85 °C (from diisopropyl ether); $[\alpha]_D^{25} = -4.3$ (*c* 1.12, $CHCl_3$); IR (nujol) 3340, 3230, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.16 (2H, d, *J* 4.8), 4.95 (1H, s), 5.25–5.94 (3H, m), 6.02 (1H, br d, *J* 4.6), 6.8–7.5 (10H, m), 8.40 (1H, br s); MS *m/z* 282 ($M^+$). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.28; H, 6.45; N, 9.88.

### 4.3. Synthesis of acyl hydrazonoyl chlorides 4

A solution of the appropriate acyl hydrazide **3** (4.5 mmol) in dry acetonitrile (45 mL) and carbon tetrachloride (3.45 g, 22.5 mmol) was treated with triphenylphosphine (5.90 g, 75 mmol) and stirred at room temperature for 12 h. Brine (25 mL) was added to reaction mixture, the organic layer separated, dried over sodium sulfate and evaporated under reduced pressure. The dark red residue was chromatographed on a silica gel column with ethyl acetate–hexane 2:1 giving hydrazonoyl chlorides **4**.

**4.3.1. Compound 4a.** 0.74 g, 73%. Yellow oil; IR (neat) 3330 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.10 (2H, d, $J$ 5.7), 4.33 (2H, s), 5.20–5.94 (3H, m), 6.9–7.3 (5H, m), 7.80 (1H, br s); MS $m/z$ 224 ($M^+$). Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.76; H, 5.80; N, 12.54.

**4.3.2. Compound 4b.** 0.47 g, 44%. Pale yellow oil; $[\alpha]_D^{25} = +13.1$ ($c$ 0.23, $CHCl_3$); IR (neat) 3325 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.47 (3H, d, $J$ 6.4), 3.98 (2H, dddd, $J$ 13.8, 7.4, 2.4, 1.8), 4.40 (1H, q, $J$ 6.4), 5.18–5.93 (3H, m), 6.9–7.3 (5H, m), 7.80 (1H, br s); MS $m/z$ 238 ($M^+$). Anal. Calcd for $C_{12}H_{15}ClN_2O$: C, 60.38; H, 6.33; N, 11.74. Found: C, 60.43; H, 6.30; N, 11.80.

**4.3.3. Compound 4c.** 0.51 g, 44%. Pale yellow oil; $[\alpha]_D^{25} = +96.7$ ($c$ 0.75, $CHCl_3$); IR (neat) 3330 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.45 (3H, d, $J$ 6.5), 1.70 (3H, d, $J$ 5.9), 3.78–4.15 (2H, m), 5.02 (1H, q, $J$ 6.5), 5.50–5.89 (2H, m), 6.9–7.3 (5H, m), 7.70 (1H, br s); MS $m/z$ 252 ($M^+$). Anal. Calcd for $C_{13}H_{17}ClN_2O$: C, 61.78; H, 6.78; N, 11.08. Found: C, 61.81; H, 6.81; N, 11.12.

**4.3.4. Compound 4d.** 0.88 g, 67%. Pale yellow powder; mp 63 °C (from methanol); $[\alpha]_D^{25} = +54.6$ ($c$ 0.80, $CHCl_3$); IR (nujol) 3340 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.14 (2H, dddd, $J$ 14.0, 7.5, 2.6, 1.8), 5.20–6.02 (3H, m), 5.35 (1H, s), 6.9–7.5 (10H, m), 7.85 (1H, br s); MS $m/z$ 300 ($M^+$). Anal. Calcd for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31. Found: C, 67.93; H, 5.73; N, 9.26.

### 4.4. Intramolecular cycloaddition of hydrazonoyl chlorides 4

A solution of the appropriate hydrazonoyl chloride **4** (2.5 mmol) in dry toluene (125 mL) was treated with triethylamine (1.01 g, 10.0 mmol) and refluxed for the time indicated in Table 1. The crude was evaporated under reduced pressure and the residue then chromatographed on a silica gel column with ethyl acetate–hexane 2:1. The first fractions contained the major cycloadduct **6**, while further elution gave minor cycloadduct **7**.

**4.4.1. Racemic cycloadduct(s) 6a and 7a.** 0.45 g, 96%. White powder; mp 66 °C (from diisopropyl ether–methanol); IR (nujol) 1605 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.30 (1H, dd, $J$ 8.0, 6.6), 3.58 (1H, dd, $J$ 6.7, 5.5), 3.75–3.90 (1H, m), 4.18 (1H, dd, $J$ 8.0, 7.8), 4.34 (1H, dd, $J$ 6.7, 6.5), 4.40 (1H, d, $J$ 9.1), 4.52 (1H, d, $J$ 9.1), 6.8–7.3 (5H, m); MS $m/z$ 188 ($M^+$). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.23; H, 6.39; N, 14.93.

**4.4.2. Major cycloadduct 6b.** 0.32 g, 64%. White powder; mp 62 °C (from diisopropyl ether); $[\alpha]_D^{25} = -24.7$ ($c$ 0.56, $CHCl_3$); IR (nujol) 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.42 (3H, d, $J$ 6.7), 3.24 (1H, dd, $J$ 8.2, 6.7), 3.54 (1H, dd, $J$ 8.0, 7.3), 3.70–3.82 (1H, m), 4.12 (1H, dd, $J$ 8.2, 8.0), 4.32 (1H, dd, $J$ 8.0, 7.7), 4.64 (1H, q, $J$ 6.7), 6.8–7.3 (5H, m); MS $m/z$ 202 ($M^+$). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.30; H, 7.02; N, 13.81.

**4.4.3. Major cycloadduct 6c.** 0.25 g, 46%. Pale yellow powder; mp 75 °C (from diisopropyl ether); $[\alpha]_D^{25} = -18.3$ ($c$ 0.31, $CHCl_3$); IR (nujol) 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.45 (3H, d, $J$ 6.5), 1.70 (3H, d, $J$ 6.5), 3.56 (1H, dd, $J$ 8.3, 6.6), 3.81–4.02 (2H, m), 4.28 (1H, dd, $J$ 8.3, 8.1), 4.58 (1H, q, $J$ 6.5), 6.8–7.4 (5H, m); MS $m/z$ 216 ($M^+$). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.14; H, 7.44; N, 13.00.

**4.4.4. Major cycloadduct 6d.** 0.26 g, 39%. Pale yellow powder; mp 88 °C (from diisopropyl ether); $[\alpha]_D^{25} = -39.7$ ($c$ 0.21, $CHCl_3$); IR (nujol) 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.39 (1H, dd, $J$ 11.5, 9.2), 3.65 (1H, s), 3.76 (1H, dd, $J$ 9.5, 7.9), 3.85–4.03 (1H, m), 4.20 (1H, dd, $J$ 9.2, 9.0), 4.52 (1H, q, $J$ 7.9, 7.7), 6.9–7.5 (10H, m); MS $m/z$ 264 ($M^+$). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.28; H, 6.07; N, 10.66.

**4.4.5. Minor cycloadduct 7b.** 52 mg, 10%. Pale yellow powder; mp 55 °C (from diisopropyl ether); $[\alpha]_D^{25} = +12.7$ ($c$ 0.28, $CHCl_3$); IR (nujol) 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 (3H, d, $J$ 6.7), 3.27 (1H, dd, $J$ 8.2, 6.7), 3.63 (1H, dd, $J$ 8.0, 7.3), 3.70–3.84 (1H, m), 4.13 (1H, dd, $J$ 8.2, 8.0), 4.24 (1H, dd, $J$ 8.0, 7.8), 4.68 (1H, q, $J$ 6.7), 6.8–7.3 (5H, m); MS $m/z$ 202 ($M^+$). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.28; H, 6.96; N, 13.80.

**4.4.6. Minor cycloadduct 7c.** 0.11 g, 20%. Pale yellow powder; mp 67 °C (from diisopropyl ether); $[\alpha]_D^{25} = +11.9$ ($c$ 0.51, $CHCl_3$); IR (nujol) 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.41 (3H, d, $J$ 6.5), 1.69 (3H, d, $J$ 6.4), 3.51 (1H, dd, $J$ 8.3, 6.6), 3.80–3.94 (2H, m), 4.32 (1H, dd, $J$ 8.3, 8.1), 4.63 (1H, q, $J$ 6.4), 6.8–7.3 (5H, m); MS $m/z$ 216 ($M^+$). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.13; H, 7.42; N, 12.89.

## Acknowledgements

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