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An Efficient Cyanide-Free Approach towards 1-(2-Pyridyl)isoquinoline-3-carbonitriles *via* the Reaction of 5-Phenacyl-1,2,4-triazines with 1,2-Dehydrobenzene in the Presence of Alkyl Nitrites

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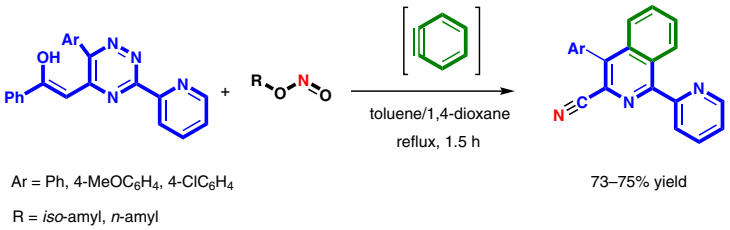

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Abstract A cyanide-free method for the preparation of 1-(2-pyridyl)isoquinoline-3-carbonitriles (3-cyanoisoquinolines) was developed. The interaction of 5-phenacyl-3-(2-pyridyl)-1,2,4-triazines with 1,2-dehydrobenzene generated *in situ* from anthranilic acid and an excess of amyl nitrites afforded the target compounds in good yields. The proposed mechanism involves the *in situ* transformation of the 5-phenacyl group into the 5-cyano group under the action of alkyl nitrite and the following inverse demand aza-Diels–Alder reaction of thus formed 5-cyano-1,2,4-triazines with 1,2-dehydrobenzene affording the target products. The presence of the 5-phenacyl substituent is a key for the reaction, as in case of 5-styryl- or 5-phenylethynyl-3-(2-pyridyl)-1,2,4-triazines the formation of the 1,2,4-triazine ring-transformation products was observed

Key words 1-(2-pyridyl)isoquinoline-3-carbonitriles, cyanide-free, aryne, inverse demand aza-Diels–Alder reaction, alkyl nitrites

Aryne-mediated transformations have become a versatile tool for the one-pot synthesis of various organic compounds and materials: from natural products[1a,b] to chemosensors[1c–f] and organic electronics components.[1g–i] Additionally, various types of Diels–Alder substrates are commonly used for the synthesis of aza-heterocyclic ligands and their annelated derivatives involving (hetero)arynes and various heterocyclic substrates.[2] However, reaction between arynes and substituted 1,2,4-triazines or 1,2,4,5-tetrazines afforded (benzo)isoquinolines[3] or their aza analogues in one-pot.[4] Recently, it was reported that in case of 1,2,4-triazines, depending on the type of the substituents in both the 1,2,4-triazine ring and the aryne core along with 'classical' Diels–Alder products, namely (aza)isoquinolines,[3,4] the reaction may afford the 1,2,4-triazine core rearrangement products, such as triazolopyrido[1,2-*a*]indoles[5] or triazolopyrimido[1,2-*a*]indoles.[6] For instance, Diels–Alder products, namely isoquinolin-3-carbonitriles, were mostly formed if the strong electron-withdrawing cyano group was present at the C5 position of the 1,2,4-triazine core,[3c] and this cyano group is commonly introduced into 1,2,4-triazines or their 4-oxides *via ipso* substitution,[7,8] or, less commonly, S_NH processes[9,10] by the reaction of different sources of CN^-. Most of the cyanides are known as fast-acting poisons; therefore alternative methods for cyano-group introduction are in high demand. In literature, a few transformations of other functional groups into cyano groups in 1,2,4-triazines have been described, such as 6-carbamoyl-[11] or 5-ketoxyme[12] groups. The direct cyanidation of isoquinoline *N*-oxides afforded the isoquinoline-3-carbonitriles in low yields,[13] and only few approaches were reported based on *ipso* cyanation,[14,15] transformation of other functional groups into the cyano one,[16] as well as the direct heterocyclization of cyano-substituted synthons.[17]

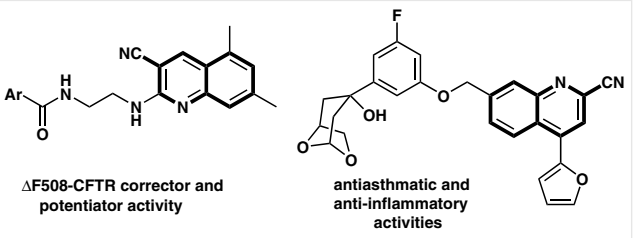
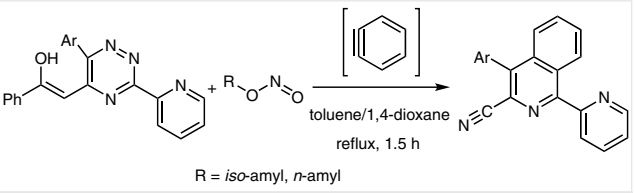


Figure 1 Representative examples of biologically active cyanoquinolines

Cyano-substituted (iso)quinolines exhibit important biological activities, such as antiasthmatic and anti-inflammatory,[16] corrector–potentiator activity in ΔF508 cystic fibrosis transmembrane conductance regulator protein,[18,19] antidiabetic activity,[20] etc. (Figure 1). In addition, the cyano group in (benzo)pyridines could be easily converted into other functionalities, such as aminomethyl[19] or carboxylic groups.[17] Herein, we wish to report a convenient cyanide-free approach for the synthesis of 1-(2-pyridyl)-isoquinolin-3-carbonitriles (3-cyanoisoquinolines) by the reactions of 5-phenacyl-3-(2-pyridyl)-1,2,4-triazines with arynes in the presence of *n*-amyl nitrite or *iso*-amyl nitrite (Scheme 1).



Scheme 1 Synthesis of 1-(2-pyridyl)isoquinoline-3-carbonitriles

For the initial step, the starting materials 1,2,4-triazines **1** (Scheme 2, R = OH) were prepared according to the previously described procedures starting from 5-phenylethynyl-1,2,4-triazines **2** by boiling in aqueous acetic acid[21] (Scheme 2, path *ii*) or by the reaction between 5-*H*-1,2,4-triazine-4-oxides **3** and acetophenone[22] (Scheme 2, path *iii*). 1,2,4-Triazine **4a** (R = H) was also synthesized according to the previously reported[23] method starting from 6-phenyl-3-(2-pyridyl)-1,2,4-triazine **5**. Based on the ^{1}H NMR data, the compounds **1a–c** and **1e** exist in one tautomeric form, as indicated in Scheme 3, while the compound **1d** bearing the 2-thienyl moiety in the C3 position of the 1,2,4-triazine moiety exists in two tautomeric forms (see Supporting Information for details). Finally, interaction with 1,2-dehydrobenzene afforded the corresponding 1-(2-pyridyl)isoquinoline-3-carbonitriles **6** in up to 75% yield[24] (Scheme 2, path *v*).[5] The structures of the products **6** were confirmed based on ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry. Finally, all the spectral characteristics of product **6a** fully correspond to those previously published data for this compound obtained by the alternative method.[25] It is worthy to mention that in our experiments neither 5-styryl- nor 5-phenylethynyl-1,2,4-triazines afforded the desired cyanoisoquinolines **6**, and in all cases the 1,2,4-triazine ring-transformation products, i.e., triazolopyrido[1,2-*a*]indoles **7** and **8** were isolated as the only products. The structures of the compounds **7** and **8** were confirmed based on the same set of methods as for compound **6**. For instance, in the ^{13}C NMR spectra of compound **7** two resonance peaks were observed in the region of δ = 76.7 and 102.4 ppm for the *sp*-hybridized carbon atoms of the phenylacetylene moiety.

Additionally, single-crystal X-ray data were collected for the rearrangement product **8** (Figure 2).[26] According to the XRD data two independent molecules are crystallized in the centrosymmetric space group (see Figure S1, Supporting Information).

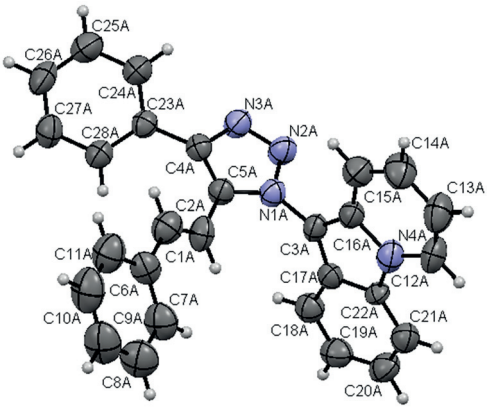
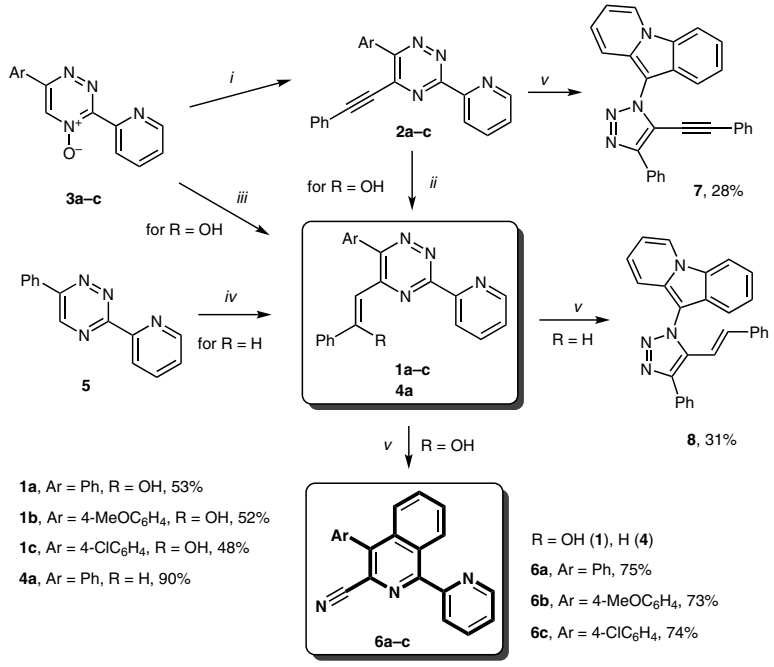


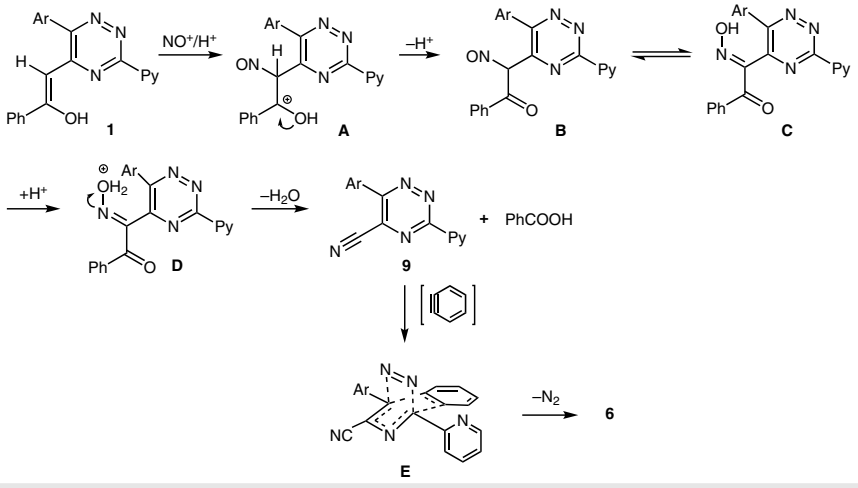
Figure 2 Crystal structure of the 1,2,4-triazine ring rearrangement product **8**

Scheme 3 represents a possible mechanism for the formation of cyanoisoquinolines **6**. According to a commonly accepted mechanism for the nitrosation of ketones,[23] on the first stage, nitrosation takes place at the double bond of the enol form of triazine **1** to afford the nitroso-substituted intermediate **A**, followed by the elimination of proton that affords nitroso derivative **B**. The isomerization of **B** followed by protonation affords the unstable intermediate **D**, and its Beckmann-type rearrangement with the elimination of benzoic acid molecule led to the cyano-1,2,4-triazine **9**. At the final step, due to the presence of the electron-withdrawing cyano group at the C5-position, the classical aza-Diels–Alder reaction is preferably realized to afford the desired 3-cyanoisoquinolines **6**.[25]

To support the proposed mechanism, the starting 5-phenacyl-1,2,4-triazines **1b–f** were treated with *iso*-amyl nitrite in the presence of 0.1–1.0 equiv of benzoic acid instead of anthranilic acid (*o*-aminobenzoic acid) under the similar reaction conditions (Scheme 4). Quite expectedly, the corresponding 5-cyano-1,2,4-triazines **9b–f** were isolated in 60–65% yield (Scheme 4). It is worthy to mention

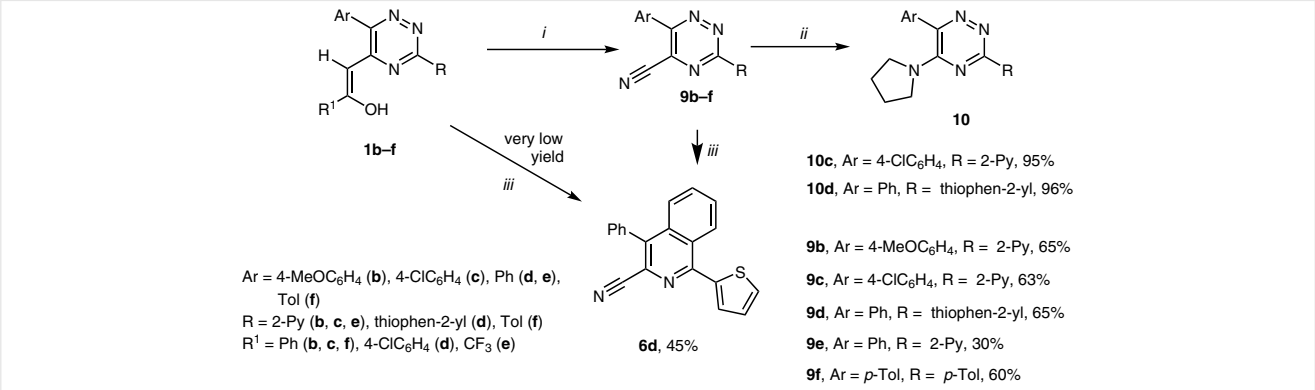


Scheme 2 The general scheme for the cyanide-free synthesis of 1-(2-pyridyl)isoquinoline-3-carbonitriles **6**. *Reagents and conditions*: *i*) Ph-acetylene, *n*-BuLi, –78 °C, 20 min, then MeCOCl; *ii*) AcOH/H_2O, reflux, 24 h; *iii*) acetophenone, NaH, THF, –20 °C, 3.5 h, then AcOH; *iv*) *n*-BuLi, phenylacetylene, THF/toluene (1:9), –78 °C, 5 min, then 20 °C, overnight, then MeOH, 20 °C; *v*) *iso*-amyl nitrite, anthranilic acid, toluene/1,4-dioxane (5:1), reflux, 1.5 h.



Scheme 3 Plausible reaction pathways

that replacing the substituents at the C3 position of the 1,2,4-triazine moiety by the thiophen-2-yl or *p*-tolyl residue (**1d** and **1f**), as well as the introduction of the other cyano-group precursors, for instance, 4-chlorosubstituted phenacyl- (**1c**) or trifluoromethyl-substituted acetonyl groups (**1e**) at the C5 position did not change the course of the reaction. However, in a last case, the conversion into the corresponding cyanotriazine was much lower (30%). The structure of the products **9** were confirmed based on ^{1}H NMR, ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. For compounds **9b**, **9e**,[27] and **9d**[25] the spectral data were compared with previously reported data (where the syntheses were carried out using other approaches).



Scheme 4 The control experiments. *Reagents and conditions*: *i*) AmONO (2 equiv), $C_6H_5CO_2H$ (0.1–1.0 equiv), toluene, reflux, 2 h; *ii*) pyrrolidine (1.25 equiv), reflux, 2 h; *iii*) *iso*-amyl nitrite, anthranilic acid, toluene/1,4-dioxane (5:1), reflux, 1.5 h.

Additionally, the structure of the product **9f** was confirmed based on the single-crystal X-ray data (Figure 3).[28] According to received data, this compound is crystallized in the chiral space group of the orthorhombic system. The chirality is ensured by the rotation of the *p*-tolyl substituents toward the heterocycle (the *p*-tolyl substituent at C6 is turned toward triazine at an angle of 45°) and by crystal packing of the obtained rotamers. The measured C≡N bond length is 1.144 Å, which is longer than in 3,6-diphenyl-1,2,4-triazin-5-carbonitrile (1.129 Å).[10] In the crystal the molecules of **9f** form the stacked molecular architectures, presumably due to the π–π interactions. The average distances between the molecular planes in the crystals of **9f** vary from 3.5 to 3.6 Å, which is a typical distance for the π–π interactions (see Figure S3, Supporting Information).

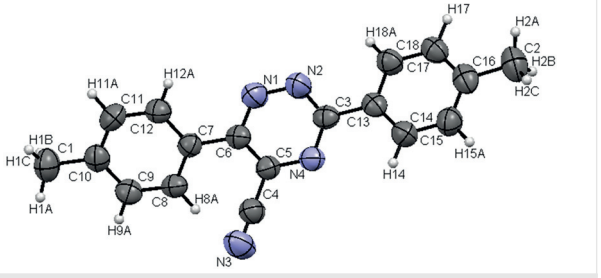


Figure 3 Crystal structure of product **9f**

Finally, the compounds **9c** and **9d** were converted into the corresponding 5-pyrrolidino-1,2,4-triazines **10** according to the previously reported procedure (Scheme 4).[29] This transformation indirectly confirms the presence of the C5-cyano group in the molecules of 1,2,4-triazines **9**, as the C5-cyano group is reported to be a good leaving group in *ipso*-substitution reactions with various nucleophiles.[10–12]

It is worthy to mention that for the 3-(2-thiphenyl)-1,2,4-triazine **1d** the one-pot reaction with anthranilic acid and *iso*-amyl nitrite afforded the target 3-cyanoisoquinoline **6d** in low yield (45%). Therefore, the reaction was carried out in two steps *via* the conversion of the C5-phenacyl group into the cyano one and followed by inverse demand aza-Diels–Alder reaction between the 5-cyano-1,2,4-triazine and benzyne. This reaction sequence was successfully demonstrated for compound **6d**.

In conclusion, we have developed a cyanide-free synthetic approach towards 1-(2-pyridyl)-substituted 3-cyanoisoquinolines starting from 5-phenacyl-1,2,4-triazines by the reaction with *in situ* generated 1,2-dehydrobenzene in the presence of alkyl nitrites. The reaction proceeds *via* nitrosation of the 5-phenacyl substituent followed by Beckmann-type rearrangement into the 5-cyano functionality, and the inverse demand aza-Diels-Alder reaction between the 5-cyano-1,2,4-triazine and 1,2-dehydrobenzene. The presence of the 5-phenacyl substituent is crucial for the reaction, as in case of 5-styryl- or 5-phenylethynyl-3-(2-pyridyl)-1,2,4-triazines the formation of the 1,2,4-triazine ring-transformation products was observed.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590961.

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(24) **Representative Synthetic Procedure for 4-Arylisoquinoline-3-carbonitriles 6**

Corresponding 1,2,4-triazines **1**, **4**, or **9d** (1.0 mmol) were suspended in dry toluene (60 mL). *iso*-Amyl nitrite or *n*-amyl nitrite (0.47 mL, 3.5 mmol) was added at once. The resulting mixture was stirred under reflux while the solution of anthranilic acid (3.5 mmol) in dry 1,4-dioxane (15 mL) was added dropwise for 30 min. The reaction mixture was heated under reflux for an additional hour and then cooled to room temperature. After that the reaction mixture was washed with 3 M aq KOH solution (3 × 50 mL), dried with anhydrous Na_2SO_4. After the filtration and evaporation of the solvents under reduced pressure the obtained residue was purified by column chromatography (silica gel) using the corresponding eluent.

1-(Pyridin-2-yl)-4-phenylisoquinoline-3-carbonitrile (6a)

Eluent: DCM/EtOAc (3:1); R_f = 0.4; yield 230 mg (75%); mp 171–173 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.53–7.60 (m, 3 H, Ph), 7.62–7.69 (m, 3 H, Ph, H-5 (py)), 7.72–7.76 (m, 1 H, isoquin.), 7.82–7.87 (m, 2 H, isoquin.), 8.06 (ddd, 1 H, *J* = 7.8, 7.8, 2.0 Hz, H-4 (py)), 8.12 (dd, 1 H, *J* = 7.8, 0.8 Hz, H-3 (py)), 8.80 (dd, 1 H, *J* = 4.8, 2.0 Hz, H-6 (py)), 8.90–8.94 (m, 1 H, isoquin.). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.6, 123.9, 125.4, 125.6, 126.5, 127.5, 128.6, 128.9, 129.4, 130.1, 130.2, 131.4, 133.8, 135.9, 137.3, 140.5, 148.7, 157.0. IR (neat): 2227 cm^{-1} (CN). MS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{14}N_3^+$: 308.12; found: 308.12. Anal. Calcd (%) for $C_{21}H_{13}N_3$: C, 82.07; H, 4.26; N, 13.67. Found: C, 81.88; H, 4.03; N, 13.32.

4-(4-Methoxyphenyl)-1-(pyridine-2-yl)isoquinoline-3-carbonitrile (6b)

Eluent: DCM/EtOAc (3:1); R_f = 0.5; yield 246 mg (73%); mp 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, OMe), 7.13 (m, 2 H, 4-MeOPh), 7.48 (m, 3 H, 4-MeOPh, H-5 (py)), 7.75 (m, 2 H, isoquin.), 7.85 (m, 1 H, isoquin.), 7.97 (ddd, 1 H, *J* = 7.8, 7.8,

2.0 Hz, H-4 (py)), 8.13 (dd, 1 H, *J* = 7.8, 0.8 Hz, H-3 (py)), 8.82 (m, 2 H, H-6 (py), isoquin.). IR (neat): 2228 cm^{-1} (CN). MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}N_3O^+$: 387.10; found: 387.10. Anal. Calcd (%) for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.08; H, 4.24; N, 12.16.

4-(4-Chlorophenyl)-1-(pyridine-2-yl)isoquinoline-3-carbonitrile (6c)

Eluent: DCM/EtOAc (3:1); R_f = 0.4; yield 252 mg (74%); mp 180–182 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.51 (m, 3 H, H-5 (py), 4-chlorophenyl), 7.59 (m, 2 H, 4-chlorophenyl), 7.72–7.82 (m, 3 H, isoquin.), 7.97 (ddd, 1 H, *J* = 7.8, 7.8, 2.0 Hz, H-4 (py)), 8.13 (dd, 1 H, *J* = 7.8, 0.8 Hz, H-3 (py)), 8.81 (dd, 1 H, *J* = 4.8, 2.0 Hz, H-6 (py)), 8.87 (m, 1 H, isoquin.). IR (neat): 2226 cm^{-1} (CN). MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{13}ClN_3^+$: 342.08; found: 342.08. Anal. Calcd (%) for $C_{21}H_{12}ClN_3$: C, 73.79; H, 3.54; N, 12.29. Found: C, 73.62; H, 3.38; N, 12.38.

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(26) Further information can be found in the CIF file. CCDC 1558492 contains the supplementary crystallographic data for compound **8**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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