One Step Synthesis of a Fused Four-Ring Heterocycle

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Complete List of Authors:	Solomos, Marina; Georgetown University, Department of Chemistry Bertke, Jeffery; Georgetown University, Department of Chemistry Swift, Jennifer; Georgetown University, Department of Chemistry

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One Step Synthesis of a Fused Four-Ring Heterocycle

Marina A. Solomos,[a] Jeffery A. Bertke[a] and Jennifer A. Swift *[a]

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A wide range of natural biomolecules and pharmaceuticals are nitrogen rich heterocycles. Though preparation of fused multi-ring systems typically requires multiple synthetic steps, 13-imino-7,13-dihydro-6H-quinazolino[3,4-a]quinazolin-6-one (IDQQ) was serendipitously obtained in one step from commercially available phenylic precursors. Single crystal X-ray diffraction, 1H-NMR and density functional theory calculations (DFT/B3LYP/6-31G(d,p)) were used in combination to unambiguously assign the major tautomer present in the monoclinic crystals. IDQQ appears to be the product of a thermodynamically-driven solution rearrangement of a key intermediate, 1,3-bis(o-cyanophenyl)urea. This type of cyclization may be an efficient method for the formation of other related heterocycles.

Introduction

Synthetic strategies for the preparation of quinazolinones and quinazolines and their pharmacological properties have been the subject of several reviews.[1-6] While the synthesis of such complex heterocycles usually requires multiple synthetic and purification steps,[7,8] the fused four-ring compound reported here, 13-imino-7,13-dihydro-6H-quinazolino[3,4-a]quinazolin-6-one (IDQQ), was obtained in high yield from a one-step reaction between simple phenylic precursors.

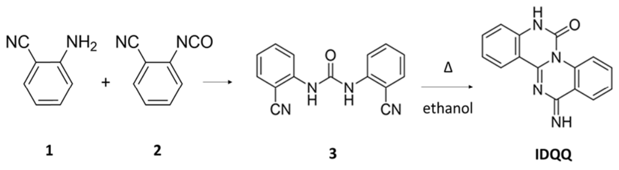
This reaction was discovered in the course of structural studies on various substituted diphenylureas (PUs). PUs are an interesting class of molecules for a variety of reasons including but not limited to their propensity to crystallize in a variety of polymorphic, cocrystal, and/or solvated phases.[9-15] Typically PUs are prepared by coupling a substituted phenylisocyanate and aniline, and harvesting the precipitate which readily forms in solution. Of the numerous PUs we have prepared to date, 1,3-bis(o-cyanophenyl)urea proved to be particularly difficult to obtain. Although colorless prisms of this compound were eventually grown,[15] its crystal structure was also atypical of PUs in that it exhibited no intermolecular N…H-N or O…H-N hydrogen bonding despite having both donor and acceptor groups. In our efforts to recrystallize the initial reaction precipitate, an unexpected color change was observed in solution, followed by the precipitation of yellow IDQQ crystals.

Using single crystal X-ray diffraction in conjunction with 1H-NMR and density functional theory calculations, the major tautomer in the IDQQ crystal structure was identified. Mechanistic studies indicated that IDQQ is the product of a intramolecular rearrangement of 1,3-bis(o-cyanophenyl)urea which occurs in solution but not in the solid state. Though other heterocyclization reactions have been reported to proceed via a radical mechanism,[7,8] IDQQ likely forms through a non-radical pathway.

Experimental

Synthesis of 13-imino-7,13-dihydro-6H-quinazolino[3,4-a]quinazolin-6-one (IDQQ)

The synthesis of IDQQ was accomplished as shown in Scheme 1. Equimolar (2 mmol) amounts of 2-aminobenzonitrile (**1**, Sigma-Aldrich) and 2-cyanophenyl isocyanate (**2**, Combi Blocks) were dissolved in a stirring solution of 1:1 (v/v) benzene:acetonitrile (100 mL) flushed with nitrogen. With continuous stirring for 7 days, an off-white precipitate formed, corresponding to 1,3-bis(o-cyanophenyl)urea (**3**, refcode: QAYXAS).[15] During recrystallization in hot ethanol, the initially colorless solution turned bright yellow. Upon cooling, yellow needle crystals corresponding to IDQQ were obtained. Recrystallization attempts in other protic and aprotic solvents also yielded IDQQ yellow needles. 1H NMR (DMSO-d6) δ 11.10 (s, 1H), 9.05 (s, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.99 (dd, J = 20.2, 8.1 Hz, 1H), 7.86 – 7.75 (m, 1H), 7.72 – 7.52 (m, 3H), 7.28 – 7.11 (m, 2H). An additional singlet at δ 9.43 ppm was also observed. IDQQ decomposes between 272-274°C.



Scheme 1 Preparation of IDQQ.

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[a] *Department of Chemistry, Georgetown University, 37th and O Sts. NW, Washington, DC 20057-1227, USA. E-mail: jas2@georgetown.edu.*

† Electronic Supplementary Information (ESI) available: [1H-NMR, TGA, DSC, Raman and cif files]. See DOI: 10.1039/x0xx00000x

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Characterization Methods

1H-NMR data were collected on a 300 MHz Varian Inova Spectrometer. A TA Instruments Modulated DSC 2920 and TA Instruments TGA Q50 were used for thermal characterization. DSC samples were prepared in hermetically sealed aluminum pans using 2-10 mg of IDQQ. All runs were performed at a heating rate of 5-10°C/min. TGA was performed in open pans using ~7 mg samples and a nitrogen flow rate of 5mL/min. PXRD data was collected on bulk ground samples at room temperature (5-40° in 2θ) on a Rigaku Ultima IV X-ray diffractometer (Cu Kα radiation, 40kV tube voltage, 30mA current). Raman spectra were collected using a Horiba LabRAM HR Evolution with a 532 nm laser and an 1800 l/mm grating filter. The beam focus was set between 50-100% to optimize signal with laser power set from 3-25%. UV absorbance spectra were obtained using Thermo Scientific NanoDrop 2000c.

Computation

Each tautomer was geometry optimized using GAUSSIAN16 at the B3LYP/6-31G(d,p) level. The input files for the total energy calculations for Tautomer I and **3** were prepared from atomic coordinates. Input files for Tautomers II - IV were prepared from modified atomic coordinates of Tautomer I.

Single Crystal Structure Determination

A single crystal of IDQQ, [$C_{15}H_{10}N_4O$], was mounted on a Mitegen micromount in mineral oil. Data (Table 1) were collected at 100(2) K on a Bruker D8 Quest equipped with a Mo IµS source and a Photon100 CMOS detector. A series of ϕ- and ω-scans were collected (monochromatic Mo Kα radiation, λ = 0.7107 Å) using the APEX2 software suite and integrated with the Bruker SAINT program.[16] Structure solution and refinement was performed using SHELX[17] and shelXle[18] software packages. Intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction was applied using Blessing's method as incorporated into the program SADABS. Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealized positions. N-H hydrogens were assigned to positions with the highest residual electron density. These positions were also consistent with the calculated 1H NMR chemical shifts and relative tautomer energies.

The structure model developed included a highly disordered, partially occupied ethanol molecule which was removed using the SQUEEZE function in PLATON.[19] The amount of electron density removed from the model corresponded to one ethanol solvent molecule with an occupancy of ~38%. This occupancy is consistent with TGA data. CCDC deposition no. 1819778

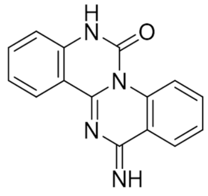
Results and discussion

IDQQ Tautomers

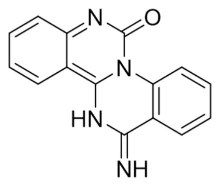
The discovery of IDQQ was in large part serendipitous – and noticeable due to the color change observed during recrystallization of **3** from several different solvents. Single crystal X-ray diffraction of a yellow IDQQ crystal unambiguously confirmed the formation of a heterocycle and the connectivity of the heavy atoms within it. IDQQ can in principle exist in at least four tautomeric forms shown in Fig. 1, which differ only in the position of two H atoms. The position of the N-H (or O-H)

Table 1 Crystal data and structure refinement for IDQQ

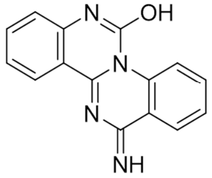
Empirical formula	$C_{15}H_{10}N_4O$
Formula weight	262.27
Temperature	102(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 4.9412(3) Å a= 90°. b = 16.3951(11) Å b= 92.079(2)° c = 16.2626(11) Å g = 90°
Volume	1316.59(15) Å3
Z	4
Density (calculated)	1.323 Mg/m3
Absorption coefficient	0.088 mm-1
F(000)	544
Crystal size	0.203 x 0.052 x 0.047 mm3
Theta range for data collection	2.783 to 25.347°
Index ranges	-5<=h<=5, -19<=k<=19, -19<=l<=19
Reflections collected	13971
Independent reflections	2401 [R(int) = 0.0781]
Completeness to theta = 25.242°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7453 and 0.5085
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2401 / 2 / 181
Goodness-of-fit on F2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0522, wR2 = 0.1368
R indices (all data)	R1 = 0.0746, wR2 = 0.1493
Extinction coefficient	n/a
Largest diff. peak and hole	0.583 and -0.543 e.Å-3



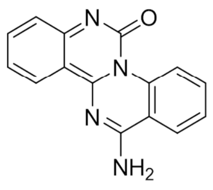
I



II



III



IV

Fig. 1 Potential tautomeric forms of IDQQ protons can be difficult to unambiguously establish with X-ray diffraction data alone. However, solution and gas phase studies provided some insight into the abundance and relative energies of the possible tautomers.

1H-NMR of IDQQ crystals dissolved in DMSO indicated that the major form in solution was tautomer I. An additional singlet at δ 9.43 ppm suggested the presence of small amounts of either tautomer IV (Fig. S1 and S2) or possibly small amounts of **3**. Gas phase energies of tautomers I-IV calculated in GAUSSIAN16 at the B3LYP/6-31G(d,p) level showed tautomer I to be the lowest in energy. Compared to I, tautomers IV, II and III are 4.69, 16.93 and 18.97 kcal/mol higher in energy, respectively. The calculated energy of **3** was also found to be higher than all IDQQ tautomers and 21.42 kcal/mol higher than tautomer I.

With knowledge of the relative tautomer energies, we took a closer look at the residual electron density in the single crystal diffraction data after all heavy atoms were assigned to identify the N-H (or O-H) atom positions. This pointed to H atoms most likely residing on the 13-imino and 7-amido N atoms, which was consistent with the lowest energy tautomer I. Although we had originally ruled out IV as the major tautomer in the crystal given the C=O bond length of 1.234 Å, small amounts of residual electron density suggested that low concentrations of tautomer IV may yet be present in the crystal.

IDQQ Structure and Properties

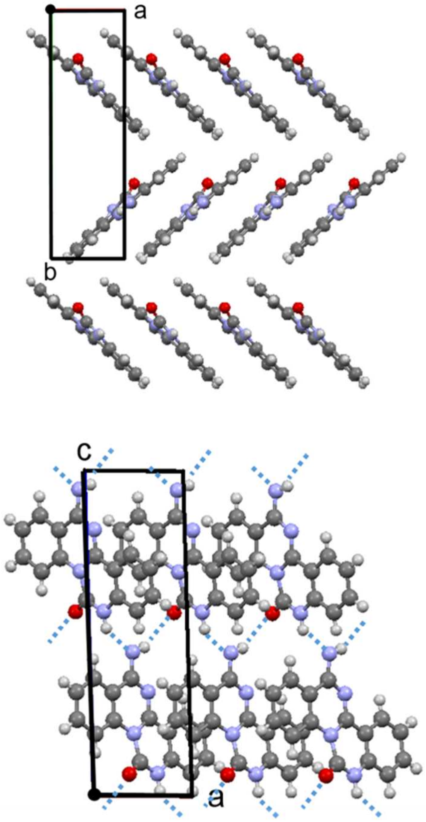
IDQQ adopts a monoclinic structure in which π-π interactions create densely packed (001) layers (Fig. 2). The center…center distance between aromatic rings along the *a*-axis is 4.941 Å. The (001) layers are connected via hydrogen bonded chains $C_2^2(6)$ which also parallel the *a*-axis. Each imino group hydrogen bonds to two molecules in the adjacent (001) layer. It serves as a hydrogen bond donor to the carbonyl of one molecule, C=N-H…O=C (N…O distance = 2.922 Å), and a hydrogen bond acceptor to the amide of another, C=N…H-N-C=O (N…N distance = 2.848 Å).

The IDQQ crystal structure also contains ethanol solvent. The highly disordered and partially occupied solvent molecule was removed using the SQUEEZE function during refinement. The solvent occupancy was refined to 38%, which was consistent with TGA data which showed a gradual ~6% weight loss between 65°C and 154°C (Fig. S3). Six percent weight loss corresponds to a 1.0:0.4 ratio of IDQQ:ethanol. Desolvation is also apparent in the DSC which showed a small broad transition beginning at ~113°C and no other transitions until sample decomposition at 272.42°C (Fig. S4).

A Solid-State Cyclization?

From previous work, originally colorless crystals of (**3**) examined under hot stage microscopy were known to turn yellow upon heating (Fig. 3). DSC thermograms of **3** also showed an intense exotherm at 172.37°C. The conformation of 1,3-bis(o-cyanophenyl)urea in the crystal structure of **3** is nearly planar (Fig. 4). For an intramolecular cyclization reaction to IDQQ to occur, a new bond between atoms labelled N3…C1 or N2…C15 would need to form to create the bond shared by the two heterocyclic rings. Given the separation distances between these pairs of atoms (4.78 or 4.76 Å, respectively), a solid state

Fig. 2 Crystal packing of IDQQ. (top) View down the c-axis shows the π-π stacking in the dense (001) plane. (bottom) View down the b-axis shows the hydrogen bonding between (001) planes.



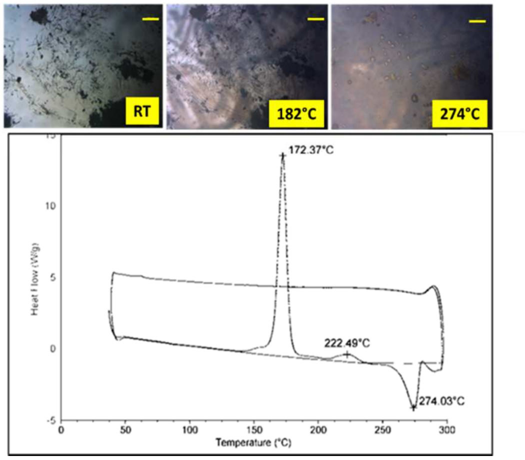


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Fig. 3 HSM micrographs and DSC thermogram of 1,3-bis(o-cyanophenyl)urea (**3**). Scale bar = 100 µm.

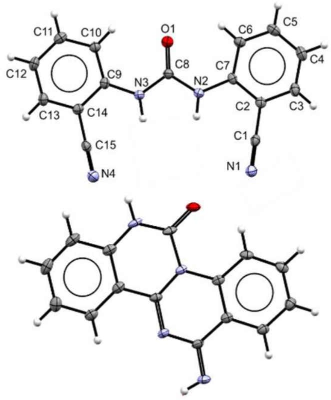

Fig. 4 Conformations of **3** (refcode: QAYXAS) and IDQQ in their respective crystal structures. Thermal ellipsoids for non-hydrogen atoms are depicted at 50% probability.

reaction seemed at least plausible since it is close to the cut-off distance for most solid state topochemical reactions.[20-23]

To assess whether the observed color change and exothermic transition in the DSC corresponded to a solid-state cyclization or simply sample decomposition, PXRD and Raman microscopy studies were performed on samples of **3** heated to 190°C, a temperature just slightly above the transition seen in DSC and HSM. PXRD patterns are compared against PXRD patterns simulated from the single crystal cif files in Fig. 5. The simulated PXRD pattern of **3** is in good agreement with that of the bulk precipitate from its initial synthesis, suggesting a single component material with reasonable phase purity (small differences in the position of some diffraction lines are due to temperature effects). PXRD patterns collected after heating to 170, 180 and 190°C show a progressive loss of diffraction intensity, and no new diffraction lines corresponding to IDQQ. This indicates **3** does not in fact undergo a solid-solid cyclization to IDQQ but that the thermal transition observed corresponds to some other phase change. Similarly, though Raman microscopy of **3** and IDQQ samples are distinguishable, samples of **3** heated to 190°C show no indication of IDQQ formation via a solid-solid cyclization reaction. Comparisons of Raman spectra are found in Fig. S5.

Solution Mechanism

Having concluded that the cyclization reaction of **3** to IDQQ must be a solution-mediated reaction, we sought to examine the effects of concentration, light and oxygen on the reaction rate. Since **3** is colorless and IDQQ is yellow, UV-Vis spectroscopy was used to monitor the development of the heterocycle product in solution over time (Fig. 6). Ethanolic solutions of **3** initially showed zero absorbance in the visible range. Ethanol solutions of dissolved IDQQ crystals had a λ_{max} = 419.5 nm. UV-Vis absorption measurements were made on 0.76 mM, 2.37 mM, and 3.94 mM solutions of **3** maintained at room temperature (24 ± 1°C) over a period of up to seven days or until the crystallization of yellow IDQQ needles was observed. An increase in absorbance at λ_{max} = 419.5 nm was seen in each sample over this time period. Using the molar absorptivity (ε = 5323.3 L mol^{-1} cm^{-1}) determined from a Beer's Law plot, the concentration of rearranged product was plotted against time. Interestingly, the least concentrated sample showed the highest absorbance increase (Fig. S6). This supports the hypothesis that heterocycle formation occurs via a unimolecular reaction, though faster precipitation of IDQQ from the more concentrated solutions of **3** may also slightly affect the relative absorption intensities.

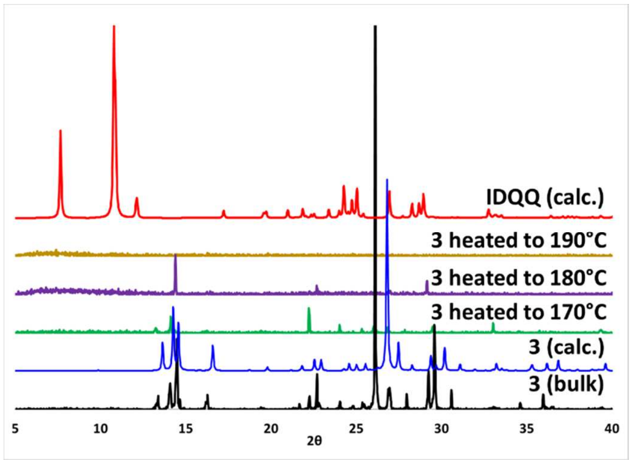

Fig. 5 PXRD of **3** (bulk precipitate at RT, simulated from cif file, and after heating to 170-190°C) and IDQQ (simulated from cif file)

Light sensitivity and O_2 experiments were next performed to assess whether the cyclization proceeds via a radical mechanism. Ethanol solutions (4mL) were purged with either O_2 or Ar before 1 mg of **3** was quickly added, then sonicated for 30 minutes. Another vial was purged with O_2 continuously for an additional 30 minutes after the addition of **3**, before sonicating for 30 minutes. All vials stored in the dark had a similar absorption at 419.5 nm after 6 hours (Fig. S7). Storage in the light or dark also made no difference in the absorbance. Since neither O_2 nor light exposure made a difference in the reaction rate, we concluded the cyclization does not occur via a radical mechanism.

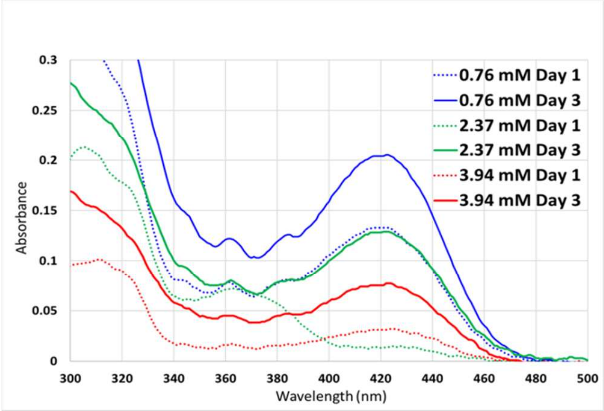

Fig. 6 UV-Vis Absorbance spectra of ethanolic solutions of **3** (0.76, 2.37 and 3.9 mM) over time. The increase in absorbance at λ_{max} = 419.5 nm with time corresponds to an increased concentration of IDQQ.

A more plausible mechanism for the rearrangement of **3** to IDQQ involves two sequential nucleophilic bond-forming steps to create the heterocycle, followed by protonation of the imino group (Fig. S8). A nucleophilic attack of N3 on C1 would close the first heterocycle ring, and the second bond-forming step between N1 and C15 would close the next heterocycle, with protonation of N4 as the final step (since **3** is symmetrical, the alternative sequence of steps would be bond formation between N2 and C15, then N4 and C1, and then N1 protonation). We presume that urea protons are sufficiently acidic to complete the final protonation step, since the rearrangement of **3** to IDQQ was found to occur in both protic and aprotic solvents.

Conclusions

The serendipitous discovery that a complex four-ring heterocycle can be prepared from simple phenylic precursors in a single step is an example of a highly efficient multi-bond forming reaction. Thermodynamic factors appear to drive the reaction, due to the high energy of 1,3-bis(o-cyanophenyl)urea (**3**), an important intermediate. The absence of hydrogen bonding in crystals of **3** is very atypical of diphenylurea compounds. By cyclizing to a lower energy heterocycle, IDQQ crystals take advantage of both extended π-π stacking and hydrogen bonding interactions. Tautomer I was calculated to have the lowest energy in the gas phase, which is also consistent with our 1H-NMR assignments in solution and the bond lengths and residual electron densities in the crystal diffraction data. Small amounts of Tautomer IV, calculated to be the second lowest in energy, may also be present in the crystal. If so, it is not clear whether this is due to the inclusion of small amounts of IV into growing crystals of I, or if it is due to intermolecular proton transfer in the solid state. The latter is at least plausible, given the short intermolecular distance carbonyl O and imino N atoms in neighboring molecules in the crystal. Since this cyclization reaction is not beholden to solid-state topochemical criteria, we presume this type of efficient multi-bond forming reaction may be a viable means to synthesize related heterocyclic compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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TOC Graphic

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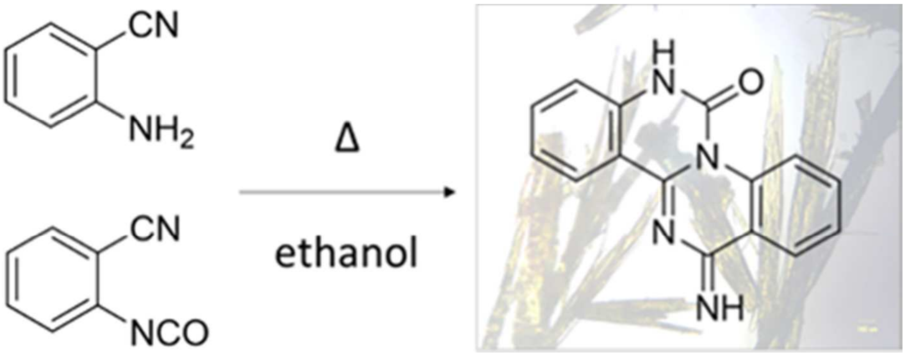
One Step Synthesis of a Fused Four-Ring Heterocycle

Marina A. Solomos, Jeffery A. Bertke, and Jennifer A. Swift
Department of Chemistry, Georgetown University, 37th and O Sts NW, Washington, DC, 20057
Correspondence email: jas2@georgetown.edu



The rearrangement of a diphenylurea to a more stable quinazolinone is confirmed through X-ray diffraction and DFT calculations.