A Pyrazole to Furan Rearrangement. Thermolysis of 5-Azido-4-formylpyrazoles

Niels Svenstrup,[†] Klaus B. Simonsen,[†] Niels Thorup,[‡] Jørgen Brodersen,[†] Wim Dehaen,[§] and Jan Becher*,[†]

Department of Chemistry, Odense University, Campusvej 55, DK-5230 Odense, Denmark, Department of Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark, and Department of Chemistry, University of Leuven, B-3001 Heverlee, Belgium

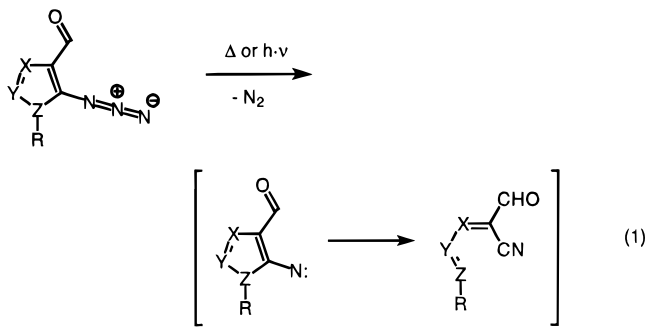
Received November 3, 1998

5-Azido-3-benzyl-4-formyl-1-phenylpyrazoles **1a**−**c** extrude dinitrogen upon heating in toluene to give the corresponding nitrenes, which immediately rearrange via a new ring-opening ring-closure reaction to produce an equimolar mixture of 4-cyano-2-phenyl-3-phenylazofurans **2a**−**c** and 3-benzyl-4-cyano-1-phenylpyrazoles **3a**−**c**. The formation of the 4-cyano-2-phenyl-3-phenylazofurans **2a**−**c** is the first example in the pyrazole series of a nitrene rearrangement, in which the parent heterocyclic system of the product differs from that of the starting material. The isolation of equimolar amounts of the two products points to the fact that their formation occurs by two mechanistically interconnected pathways, between which the exchange of a redox equivalent takes place. Evidence for the existence of two mechanistically interlinked pathways is presented, and the insight into the stoechiometry of the reaction is taken advantage of to optimize the reaction with respect to either of the two products **2** or **3**. Thus, it is demonstrated how one can bias the two pathways using external reagents, thereby changing the product distribution ratio **2**:**3** from 1:1 in the unbiased case, to 1:4 in one direction, and to better than 20:1 in the other direction.

Introduction

The thermal or photochemical rearrangement of heterocyclic azides has attracted attention as a means of constructing new heterocyclic compounds, which are otherwise inaccessible by ring synthesis or by modification of existing heterocycles.[1] The synthetic utility of this method owes itself to the characteristic ability of homo- as well as heteroaromatic nitrenes to undergo rearrangements,[1,2] in contrast to carbenes, that are more inclined to participate in addition chemistry.[3] An especially attractive variant of the heterocyclic nitrene rearrangement reaction is the ring-opening ring-closure rearrangement of heterocyclic azides,[4] since it, depending on the nature of the substituents, can provide access to new heterocyclic compounds.[5]

We have previously studied the thermal rearrangement of a variety of 5-azido-4-formyl heterocycles,[4,5] in particular the rearrangements of substituted pyrazoles.[6] An important general feature of the mechanism of these reactions is thought to be the formation of an acyclic cyanoformyl intermediate in the first step after generation of the nitrene (or nitrenoid species);[7] the acyclic cyanoformyl compound has never been isolated in the 5-azido-4-formylpyrazole thermolysis reaction, but similar intermediates have been isolated in the pyrolysis of the 5-azido-4-formylpyrazole imines[8,9] and 5-azido-4-arylpyrazoles[10,11] (Reaction 1).



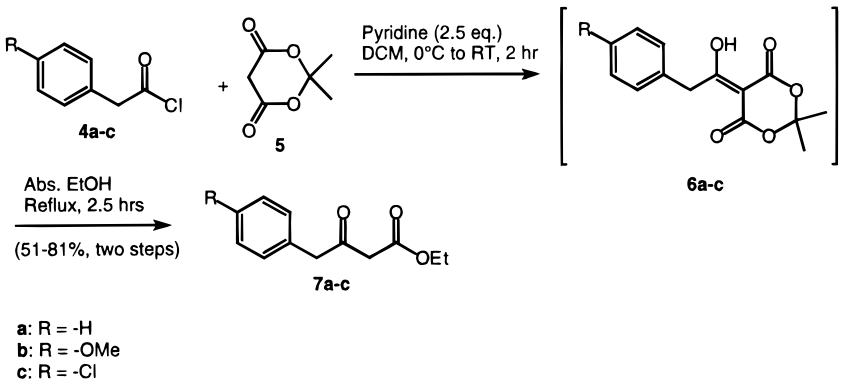
The acyclic cyanoformyl intermediate can potentially cyclize by several different pathways, depending on the reaction conditions, the atoms X, Y, and Z, the substit-

* To whom correspondence should be addressed. Tel: + 45 65 57 25 54. Fax: + 45 66 15 86 89.
† Odense University.
‡ The Technical University of Denmark.
§ University of Leuwen.

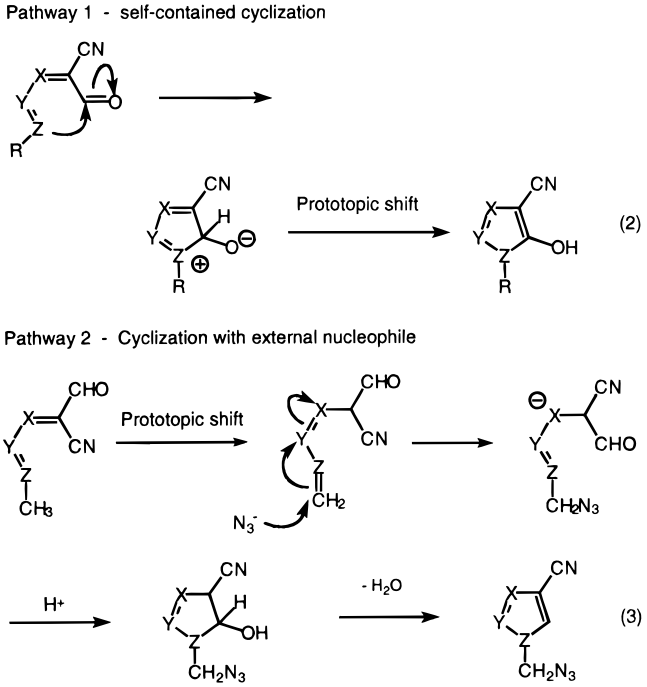
(1) For recent reviews, see: (a) Dehaen, W.; Becher, J. *Acta Chem. Scand.* **1993**, *47*, 244−254 (b) Funicello, M.; Spagnolo, P.; Zanirato, P. *Ibid.* **1993**, *47*, 231−243.
(2) L'abbé, G. *Angew. Chem.* **1975**, *87*, 831−838.
(3) Helquist, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.-in-chief; Fleming, I., Ed.; Oxford, 1991; Vol. 4, pp 951−997.
(4) (a) Becher, J.; Brøndum, K.; Krake, N.; Pluta, K.; Simonsen, O.; Molina, P.; Begtrup, M. *J. Chem. Soc., Chem. Commun.* **1988**, 541−542. (b) Pluta, K.; Andersen, K. V.; Jensen, F.; Becher, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1583−1584.
(5) Becher, J.; Jørgensen, P. L.; Pluta, K.; Krake, N. J.; Fält-Hansen, B. *J. Org. Chem.* **1992**, *57*, 2127−2134.
(6) For a comprehensive review of 1*H*-pyrazole chemistry, see: Kirschke, K. In *Methoden der Organischen Chemie (Houben-Weyl)*; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1994; Vol. E8b, Part 2, pp 399−763.
(7) For a detailed discussion of nitrene formation versus concerted ring opening of azides, see: (a) Dyall, L. K.; Suffolk, P. M.; Dehaen, W.; L'abbé, G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2115−2118. (b) L'abbé, G.; Dyall, L.; Meersman, K.; Dehaen, W. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2401−2406. (c) L'abbé, G.; Dyall, L.; Meersman, K.; Dehaen, W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2111−2118. (d) L'abbé, G.; Dyall, L. K.; Meersman, K.; Dehaen, W. *J. Chem. Res., Miniprint* **1997**, 1631−1650.
(8) Dehaen, W.; Becher, J. *Tetrahedron Lett.* **1991**, *32*, 3565−3568.
(9) Becher, J.; Begtrup, M.; Gjerløv, A.; Larsen, S.; Dehaen, W.; Christensen, L. K. *Acta Chem. Scand.* **1995**, *49*, 57−63.
(10) (a) Smith, P. A. S.; Breen, G. J. W.; Hajek, M. K.; Awang, D. V. C. *J. Org. Chem.* **1970**, *35*, 2215−2221. (b) Smith, P. A. S.; Dounchis, H. *Ibid.* **1973**, *38*, 2958−2963.
(11) Intermediates of this type have also been isolated in the 1,2,3-triazole series: Smith, P. A. S.; Krbechek, L. O.; Resemann, W. *J. Am. Chem. Soc.* **1964**, *86*, 2025−2033.

10.1021/jo9822075 CCC: $18.00
Published on Web 03/19/1999

Scheme 1



uents, and external nucleophiles. Two main pathways have been identified so far: self-contained cyclization (pathway 1, reaction 2) and cyclization under the influence of an external nucleophile (pathway 2, reaction 3).

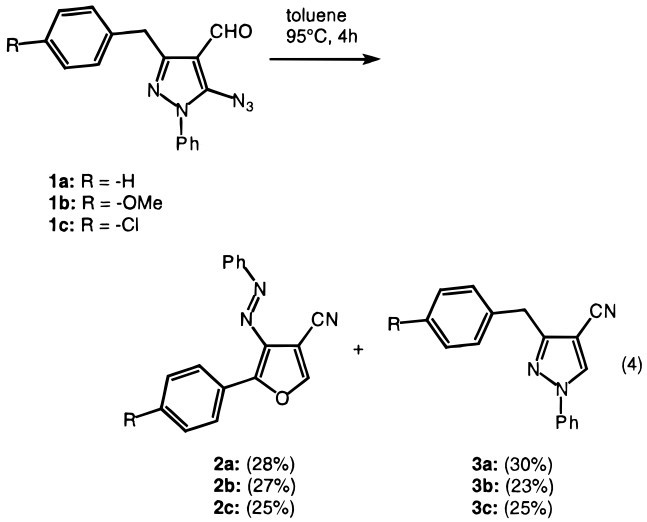


However, none of these routes provide an entry into other heterocyclic parent systems, since in all the known examples pyrazoles are converted to differently substituted pyrazoles and so forth; in this paper, the development of a new synthetic path for the synthesis of furans as well as pyrazoles by thermal rearrangement of 5-azidoformyl pyrazoles **1a**−**c** with benzylic subsitutents in the 3-position is described. In this case, two interconnected pathways operate to produce an equimolar amount of the furan **2** and the pyrazole **3** (reaction 4).

Additionally, this paper details our initial suggestion for the mechanism of this reaction and how the insight gained by this newly formulated mechanism enabled us to optimize the reaction with respect to either the furan or the pyrazole.

Results and Discussion

Azide Synthesis. The requisite 3-substituted 5-azido-4-formyl-1-phenylpyrazoles **1a**−**c** were prepared according to methodology developed in this group.[12] In the first step, Meldrum's acid **5**[13] was acylated using 1 equiv of the acid chlorides **4a**−**c** in dichloromethane with 2.5 equiv of pyridine as the base and acylation catalyst.[14] The resulting acylated Meldrum's acids **6a**−**c** were not isolated; instead they were subjected to an acidic aqueous workup to remove the pyridine and immediately thereafter refluxed in absolute ethanol for 2.5 h to give the β-ketoesters **7a**−**c** in 51−81% yield after an aqueous workup and vacuum distillation through a Claisen column (Scheme 1).



This procedure, at least in our hands, proved vastly superior to the conventional β-ketoester synthesis, in which diethyl malonate is metalated using diethoxymagnesium and alkylated using an acid chloride, after which the resulting acylmalonate is decarboxylated by heating to 250 °C in the presence of naphthalene-2-sulfonic acid monohydrate to give the desired β-ketoester.[15]

In the next step, the construction of the heterocyclic rings, the required pyrazolones **8a**−**c** were prepared by condensing phenylhydrazine with the β-keto esters **7a**−**c** using standard chemistry differing in no significant way

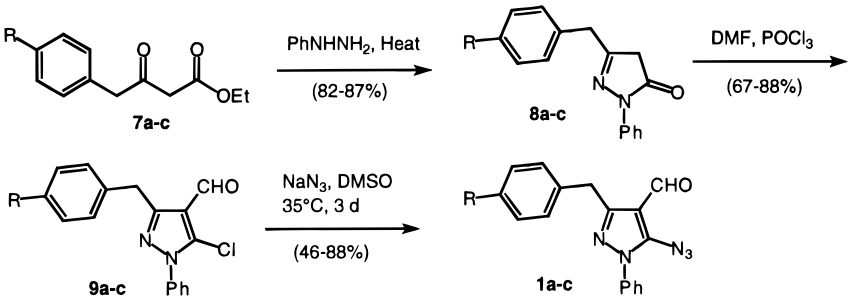
(12) Molina, P.; Arques, A.; Vinander, M. V.; Becher, J.; Brøndum, K. *J. Org. Chem.* **1988**, *53*, 4654−4663.

(13) Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426−3428.

(14) The acid chlorides **4a,b** are commercially available, whereas acid chloride **4c** was prepared by the standard procedure using thionyl chloride in toluene. See for example: Miller, W. H.; Dessert, A. M.; Anderson, G. W. *J. Am. Chem. Soc.* **1948**, *70*, 500−502.

(15) Vogel, A. I. *Textbook of Practical Organic Chemistry*; Longman Scientific and Technical: Essex, 1989; pp 742−743.

Scheme 2



a: R = -H, **b**: R = -OMe, **c**: R = -Cl

from the procedures developed by Knorr[16] in the late nineteenth century (Scheme 2).[17] The pyrazolones **8a**−**c** were then subjected to a Vilsmeier−Haack chloroformylation[18] using 3 equiv of *N*,*N*-dimethylformamide and an excess of phosphoryl chloride.[19] In some cases, the desired 5-chloro-4-formylpyrazoles crystallized directly from the reaction mixture upon addition of water to hydrolyze the intermediate and excess $POCl_3$, while in other cases, the reaction mixture had to be neutralized using solid sodium carbonate following the addition of water (Scheme 2). Finally, the 5-chloro-4-formylpyrazoles **9a**−**c** were converted to the corresponding azides **1a**−**c** by reaction with sodium azide in DMSO solution at 35 °C for 3 days in the dark (Scheme 2). The azides **1a**−**c** were obtained in analytical purity after the crude reaction mixtures were subjected to an aqueous workup followed by column chromatography on silica gel.

This nucleophilic aromatic substitution, which would be very difficult to carry out in the benzene series, proceeds smoothly, thanks partly to the electronic nature of the pyrazole ring and partly to the presence of the electron-withdrawing formyl substituent in the 4-position.[20] However, it is essential that the temperature is kept under 35 °C and all light must be excluded, as the azides are quite prone to rearrangement under the influence of both thermal and photochemical stimulation.

Azide Rearrangement. The azides **1a**−**c** were subjected to thermolysis by heating approximately 1 mmol of the azides in toluene at 95 °C for 4 h. The initially yellow reaction mixtures soon turned dark orange, and formation of two individual products was evident in thin-layer chromatography after about 30 min. Upon nearly complete disappearance of the starting material, the reactions mixtures were cooled to room temperature and evaporated in vacuo, and the resulting residues were subjected to column chromatography on silica gel to give two products, which in the case of **1a** were identified as 4-cyano-2-phenyl-3-phenylazofuran (**2a**) and 3-benzyl-4-cyano-1-phenylpyrazole (**3a**), respectively, on the basis of spectroscopic evidence (reaction 4).

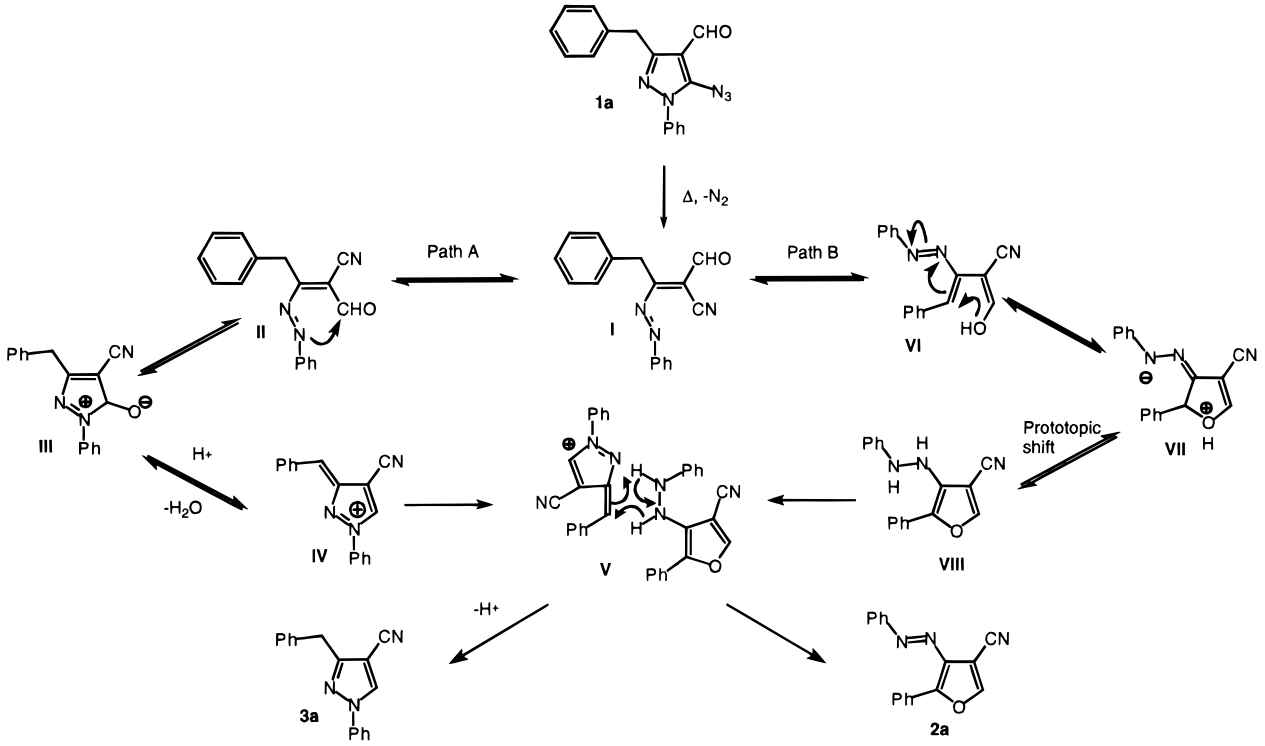
Identification of the Thermolysis Products. In the case of the thermolysis of 5-azido-3-benzyl-4-formyl-1-phenylpyrazole (**1a**), two orange compounds with R_f = 0.57 and 0.41, respectively, were formed, of which the latter displayed an intense fluorescence on the TLC plates.

The less polar compound was found to be 4-cyano-2-phenyl-3-phenylazofuran (**2a**) on the basis of the following evidence: The isolated crystalline material gave an elemental analysis consistent with the elemental composition $C_{17}H_{11}N_3O$, corresponding to the loss of one molecule of N_2 and one molecule of H_2 from the starting material **1a**. An EIMS molecular ion at m/z = 273 confirmed this. In addition, the less polar compound **2a** displayed an ^{1}H NMR spectrum, in which only aromatic resonances could be seen: integration demonstrated the spectrum to consist of signals from 11 hydrogen atoms (two phenyl substituents and 1 furan proton). The ^{13}C NMR spectrum displayed 13 individual resonances, all at δ >90, consistent with the presence two phenyl rings, an unsymmetrical trisubstituted furan ring, and a nitrile. In the IR spectrum, an intense band at 2232 cm^{-1} supported the evidence pointing to the presence of a conjugated cyano group, and the presence of the azo group was confirmed by Raman spectroscopy, in which a band at 1429 cm^{-1} was prominent, indicative of the presence of an asymmetric azo group (due to its unpolar nature, the absorption from the phenylazo substituent is absent or very weak in IR). All of these observations in unison supported the hypothesis that **2a** was the new compound 4-cyano-2-phenyl-3-phenylazofuran. The structure of the furan product was unequivocally determined by single-crystal X-ray structure analysis of the rather more crystalline methoxy-substituted analogue **2b**, which could be crystallized from a mixture of 1,2-dichloroethane and methanol.[21] The X-ray data and ORTEP diagrams for **2b** are included as Supporting Information.

The more polar compound **3a** was deduced to be 3-benzyl-4-cyano-1-phenylpyrazole on the basis of a variety of spectroscopic and physical measurements. In addition, compound **3a** gave an elemental analysis suggesting it to have the elemental composition $C_{17}H_{13}N_3$, and again this was supported by EIMS with a molecular ion peak at m/z = 293. In other words, **3a** had been formed from **1a** by the formal extrusion of both a molecule of N_2 and an oxygen atom. The ^{1}H NMR spectrum of **3a** displayed a singlet at 8.17 ppm (one proton), a multiplet spanning from 7.70 to 7.20 ppm (10 protons), and a singlet at 4.17 ppm (two protons). The ^{13}C NMR displayed 13 lines, one in the aliphatic and 12 in the aromatic region. Thus, the NMR data indicated the presence of a phenyl and a benzyl substituent, as well as the presence of a nitrile functionality and an unsymmetrical trisubstituted pyrazole ring. The IR spectrum

(16) Knorr, L. *Chem. Ber.* **1884**, *17*, 546−552.
(17) The preparation of compound **8a** has been claimed in the literature, but no spectroscopic or physical data were reported: Tietze, L. F.; Steinmetz, A.; Balkenhohl, F. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303−1306.
(18) Meth-Cohn, O.; Stanforth, S. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed-in-chief; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 777−794.
(19) Becher, J.; Olesen, P. H.; Knudsen, N. A.; Toftlund, H. *Sulfur Lett.* **1986**, *4*, 175−183.
(20) For a review of 3-chlorovinylaldehydes, see: Pulst, M.; Weissenfels, M. *Z. Chem.* **1976**, *16*, 337−348.

Scheme 3



displayed a prominent absorption at 2227 cm^{-1}, indicative of the presence of a conjugated cyano group, thus supporting this hypothesis. In combination, these observations led us to conclude that **3a** was the new heterocyclic compound 3-benzyl-4-cyano-1-phenylpyrazole. The structure of the pyrazole product was also successfully determined by single-crystal X-ray structure analysis of the more crystalline methoxy-substituted analogue **3b**.[21] This structure along with selected bond lengths and angles can be found in the Supporting Information section.

Proposed Reaction Mechanism. To explain the formation of equimolar amounts of the two products **2a**−**c** and **3a**−**c**, we formulated the following reaction mechanism (Scheme 3):

In analogy with other known azide rearrangements of pyrazoles,[4−8] we assume the first step of the reaction to be the extrusion of molecular dinitrogen from the azide, thus generating a nitrene, which immediately rearranges in what is presumed to be a concerted electrocyclic ring-opening reaction to give the acyclic intermediate **I**. In contrast to our previous systems, the benzylic CH_2 group of **I** enables it to undergo recyclization by two different paths, namely path A leading to the formation of a new pyrazole ring systems (in a way somewhat similar to most of our already described azide rearrangements) and path B leading to the formation of a furan ring in a reaction which has no precedents.

In path A, the pyrazole ring is reformed by recyclization via a nucleophilic attack of N-1 onto the formyl group as shown in structure **II** (attack onto the nitrile would reform the intermediary nitrene), thereby giving rise to a heterocyclic betaine **III**. Protonation of the betaine would allow the elimination of a molecule of water to give the presumably highly reactive intermediate **IV**. Reaction of **IV** with 1 equiv of H_2 (in the form of the easily oxidizable 1,2-disubstituted hydrazine **VIII**) or a similar redox equivalent as shown in structure **V** then reduces the betaine to the product 3-benzyl-4-cyano-1-phenylpyrazole (**3a**) after loss of a proton.

In path B, the acyclic compound **I** first tautomerizes to the vinylogous enol **VI**, the driving force presumably being the highly extended conjugation of the system. The highly electron-withdrawing effect of the phenylazo substituent causes **VI** to be quite electrophilic in the β-position relative to this group, and it therefore presumably undergoes a fast intramolecular Michael-type addition to give the furan **VII**. Two prototopic shifts cause the furan ring system to gain aromatic resonance stabilization, thus forming the *N*,*N*′-disubstituted hydrazine **VIII**, which can be assumed to have a very low oxidation potential, since oxidation to an azo group confers complete conjugation to the molecule. Transfer of one molecule of H_2 to the pyrazole **IV** in the final step of the reaction through transition state **V** completes path B, in the process generating one molecule of 4-cyano-2-phenyl-3-phenylazofuran (**2a**).

The existence of of two interconnected reaction pathways is supported by the observation that approximately equimolar amounts of the two products **2** and **3** are isolated from the reaction. To gain further insight into the progress of the reaction, it was decided to monitor the reaction by ^1H NMR: in a separate experiment, 5-azido-3-benzyl-4-formyl-1-phenylpyrazole was subjected to thermolysis in toluene at 95 °C for 4 h, during which time aliquots were taken from the reaction mixture every 15 min. ^1H NMR of these aliquots confirmed our supposition that the products **2** or **3** were being formed at what appeared to be identical rates over the 4 h that we monitored the reaction.

(21) The authors have deposited atomic coordinates and thermal parameters for **2b** and **3b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

Table 1

azide	additive	yield of **2** (%)	yield of **3** (%)
1b		27	23
1b	2,3-dichloro-5,6-dicyanoquinone	49	<1
1b	1,2-diphenylhydrazine	9	41

To provide further evidence of the mechanism of this chemical transformation, and to illuminate the scope of the reaction, we decided to attempt to influence the course of the reaction by adding external reagents. In the proposed mechanism of formation of the furan **2** (Scheme 3), a transfer of a redox equivalent from the hydrazine **VIII** is postulated, and we would therefore expect that the addition of an oxidizing agent would promote the formation of furan **2** on the expense of the pyrazole **3**. On the other hand, the mechanism of formation of the pyrazole **3** calls for the acid-catalyzed loss of water from the intermediate **III**, followed by addition of 1 equiv of dihydrogen to intermediate **IV** and subsequent loss of a proton to give the pyrazole **3**; thus, we anticipated that the addition of a suitable reducing agent, as well as a small amount of *p*-toluenesulfonic acid to accelerate the elimination of water from intermediate **III** would significantly increase the yield of pyrazole **3**, while at the same time suppressing the formation of the furan **2**.

Indeed, when the azide **1b** was subjected to thermolysis in dry toluene at 95 °C for 4 h in the presence of 1.5 equiv of the well-known oxidizing agent 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ), the furan **2b** was formed in 49% isolated yield while the formation of the pyrazole **3b** was at the same time completely suppressed (compare with 27% yield of the furan and 23% yield of the pyrazole in the native experiment). These results are summarized above (Table 1). Likewise, when the azide **1b** was reacted with the reducing agent 1,2-diphenylhydrazine (1.5 equiv) in dry toluene at 95 °C for 4 h in the prescence of a catalytic amount of *p*-toluenesulfonic acid, the pyrazole **3b** was formed in 41% yield, while the formation of the furan **2b** was markedly inhibited: only 9% of **2b** was isolated after chromatography (Table 1).

It is an interesting fact that the combined yield of the two products **2** and **3** rarely exceeds 50%, especially because no other products were ever isolated from the reaction mixture after chromatography. During the thermolysis of **1a**−**c**, a maximum yield of product is achieved under the conditions described in the Experimental Section, and prolonged heating seems to lead only to decomposition of the starting material; quite likely, the polymerization of the very reactive intermediate **I** is a competing reaction. An alternative explanation is that the reaction slows down markedly when the effective concentration of intermediate **I** drops (due to decreased amounts of starting material) as the reaction progresses: in this situation a molecule of either of the intermediates **IV** and **VIII** is less likely to encounter its respective reaction partner for the formation of the disproportionation-like transition state **V** (Scheme 3), and competing reactions not leading to the desired products **2** and **3** therefore become more dominant.

Conclusion

In this paper, we have demonstrated that highly substituted furans and pyrazoles can be formed from readily available starting materials in a few synthetic steps by thermolysis of 5-azidopyrazoles. The reaction investigated appears to involve a disproportionation-like transfer of redox equivalents from one reaction pathway to another, thereby coupling the formation of the two products. Evidence for the existence of such two interlinked pathways is as follows: In the unbiased reaction, in which no external reagents are added, the two products **2a**−**c** and **3a**−**c** are invariably formed in nearly equimolar amounts. In addition, it is possible to influence the course of the reaction by adding external redox reagents: Addition of the oxidizing agent DDQ leads to selective formation of the furan **2**, while addition of the reducing agent 1,2-diphenylhydrazine and a catalytic amount of *p*-toluenesulfonic acid to the reaction significantly favors the formation of the pyrazole **3**. Thus, under what is effectively the same conditions, it is possible to produce two different heterocycles from the same starting material by adding either an oxidizing or a reducing agent.

Experimental Section

Toluene for the thermolysis reactions was purified by distillation from sodium benzophenone ketyl and stored over 4 Å molecular sieves, and ethanol was purified by distillation from Mg under N_2 and stored over 3 Å molecular sieves. DMF and DMSO were dried by standing over 4 Å molecular sieves for at least 24 h and were not distilled prior to use. Pyridine was dried by standing over KOH overnight, after which it was distilled in vacuo. Dichloromethane (HPLC grade) was used without any prior purification. Water content of the purified solvents was checked by Karl Fischer titration of 1 mL samples of the solvents on a Metrohm Karl Fischer titration apparatus based on a Metrohm 737 KF coulometer.

All reagents employed were of standard reagent grade and purchased from Aldrich, except for Meldrum's acid (**5**), which was prepared from malonic acid and acetone following a procedure published by Davidson,[13] and 4-chlorophenylacetyl chloride (**4c**), which was prepared from the commercially available carboxylic acid by reaction with thionyl chloride in toluene.[14]

Analytical thin layer chromatography (TLC) was performed on Merck DC-Alufolien Kieselgel 60 F_{254} 0.2 mm thickness precoated TLC plates, while column chromatography was performed using Merck Kieselgel 60 (0.040−0.063 mm, 230−400 mesh). Developed TLC plates were visualized either by quenching of UV fluorescence at 254 nm or by spraying with iodine vapor. ^{1}H NMR spectra were recorded at 250 MHz or at 300 MHz using the deuterated solvent as lock and TMS or the residual solvent as internal reference. ^{13}C NMR spectra were recorded at 63 or 75 MHz, respectively, using broad band decoupling. Elemental analyses were performed at the Microanalytical Laboratory, University of Copenhagen, Denmark.

Warning! Although no problems were experienced in this study, heterocyclic azido compounds are potentially explosive, and care should be taken in their handling and storage.

Ethyl Phenylacetoacetate 7a. General Procedure for 7a−**c.** To a solution of Meldrum's acid **5** (21.8 g, 0.151 mol) in CH_2Cl_2 (60 mL) in a 250 mL round-bottomed flask, equipped with an addition funnel and nitrogen inlet and cooled to 0 °C, was added pyridine (30 mL) over a period of 10 min. To this solution was then added a solution of freshly distilled phenylacetyl chloride **4a** (22.8 g, 0.147 mol) in CH_2Cl_2 (45 mL), which resulted in an orange solution. After the addition was complete (approximately 2 h), the resulting dark orange solution was stirred for 1 h at 0 °C, allowed to warm to room temperature, and stirred for an additional hour. The solution was diluted with CH_2Cl_2 (50 mL) and poured onto 2 M HCl and ice. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with 2 M HCl (2 × 50 mL) and brine (100 mL), dried over Na_2SO_4, and evaporated. The resulting orange crystals,

which mainly consisted of the acetylated Meldrum's acid, were suspended in EtOH (300 mL) in a 500 mL round-bottomed flask and refluxed for 2.5 h. The solvent was removed in vacuo, leading to a dark oil. Distillation under reduced pressure gave 24.5 g (81%) of **7a** as a clear oil: bp 88 °C (0.07 mbar); ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 5H), 4.17 (q, J = 7.1 Hz, 2H), 3.82 (s, 2H), 3.44 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H).[22]

Ethyl 4-Methoxyphenylacetoacetate (7b). Compound **7b** was prepared as described for **7a** using Meldrum's acid **5** (15.0 g, 0.104 mol) and 4-methoxyphenylacetyl chloride (**4b**) (18.28 g, 0.099 mol). Distillation under reduced pressure gave 11.90 g (51%) of **7b** as a clear oil: bp 95−98 °C (0.07 mbar); ^{1}H NMR ($CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 3.55 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Ethyl 4-Chlorophenylacetoacetate 7c. Compound **7c** was prepared as described for **7a** using Meldrum's acid **5** (11.0 g, 0.076 mol) and 4-methoxyphenylacetyl chloride **4c** (14.0 g, 0.081 mol). Distillation under reduced pressure gave 11.2 g (57%) of **7c** as a clear oil: bp 115 °C (0.07 mbar); ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.80 (s, 2H), 3.45 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H).

3-Benzyl-1-phenyl-5-pyrazolone (8a). To a well-stirred solution of ethyl phenylacetoacetate **7a** (26.7 g, 0.115 mol) in 60% EtOH (12 mL) was added dropwise phenylhydrazine (12.1 g, 0.112 mol) at such a rate that the temperature was kept below 50 °C (approximately 30 min). The yellow reaction mixture was stirred at room temperature for 2 h, refluxed for 4 h, and finally allowed to cool to room temperature and poured into a mixture of H_2O/ice (100 mL) containing two drops of concentrated HCl. The resulting yellow solid was filtered, washed with H_2O (3 × 100 mL), and dried. Recrystallization from 96% EtOH gave 23.5 g (82%) of **8a** as white crystals: mp 134−135 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 7.7 Hz, 2H), 7.4−7.1 (m, 8H), 3.82 (s, 2H), 3.33 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.6, 158.7, 138.1, 135.6, 129.1, 128.9, 128.8, 127.5, 125.2, 119.0, 41.0, 37.9; MS (EI) m/z 250 (M^+, 100); IR (KBr) ν 1714, 1690 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.75; H, 5.61; N, 11.36.

3-(4-Methoxybenzyl)-1-phenyl-5-pyrazolone (8b). Compound **8b** was prepared as reported for **8a** using ethyl 4-methoxyphenylacetoacetate (**7b**) (9.69 g, 0.041 mol) and phenylhydrazine (4.43 g, 0.041 mol). Recrystallization from 96% EtOH gave 9.58 g (84%) of **8b** as white crystals: mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.25 (m, 3H), 6.88 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 2H), 3.32 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.3, 158.7, 147.2, 137.6, 128.5, 127.9, 127.2, 126.2, 123.4, 114.5, 55.1, 40.9, 36.9; MS (EI) m/z 280 (M^+, 100); IR (KBr) ν 1714, 1693 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 72.84; H, 5.75; N, 9.99. Found: C, 76.75; H, 5.61; N, 11.36.

3-(4-Chlorobenzyl)-1-phenyl-5-pyrazolone (8c). Compound **8c** was prepared as reported for **8a** using ethyl 4-chlorophenylacetoacetate (**7c**) (11.17 g, 0.046 mol) and phenylhydrazine (5.02 g, 0.046 mol). Recrystallization from 96% EtOH gave 11.40 g (87%) of **8c** as white crystals: mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 2H), 7.5−7.1 (m, 7H), 3.79 (s, 2H), 3.32 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 165.5, 151.5, 138.1, 137.9, 130.8, 130.3, 128.8, 128.1, 125.6, 120.9, 87.6, 33.5; MS (EI) m/z 284 (M^+, 100); IR (KBr) ν 1714, 1690 cm^{-1}. Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.48; H, 4.56; N, 9.84.

3-Benzyl-5-chloro-4-formyl-1-phenylpyrazole (9a). DMF (11.0 g, 0.15 mol) was poured into a 250 mL three-necked round-bottomed flask equipped with a mechanical stirrer, addition funnel, and thermometer and cooled to 0 °C on an ice bath. To the reaction flask was slowly added $POCl_3$ (32 mL, 0.35 mol) at such a rate that the temperature was maintained below 10 °C (mechanical stirring is essential in this step to prevent the reaction mixture from becoming solid midway through the addition, thus causing the temperature to rise out of control). Then 3-benzyl-1-phenyl-5-pyrazolone (**8a**) (12.5 g, 0.05 mol) was added in small portions, and the resulting solution was stirred at room temperature for 30 min and at 100 °C for 1 h. The dark reaction mixture was cooled to room temperature and poured slowly onto ice/H_2O (75 mL) and neutralized to pH 6−7 by adding Na_2CO_3 in small portions. The resulting brown solid was filtered and washed with H_2O. Recrystallization from EtOH gave 9.94 g (67%) of **9a** as yellow plates: mp 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 9.95 (s, 1H), 7.6−7.1 (m, 10H), 4.31 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 183.5, 154.1, 129.3, 129.2, 129.1, 128.4, 126.5, 125.3, 116.9, 33.8; MS (EI) m/z 296 (M^+, 100); IR (KBr) ν 1679, 1523 cm^{-1}. Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.76; H, 4.39; N, 9.42.

5-Chloro-4-formyl-3-(4-methoxybenzyl)-1-phenylpyrazole (9b). Compound **9b** was prepared as for **9a** above employing 3-(4-methoxybenzyl)-1-phenyl-5-pyrazolone (**8b**) (8.72 g, 0.031 mol). The product crystallized immediately upon being poured into water, thus allowing it to be isolated by filtration. After the product was washed thoroughly on the filter with water and air dried, the crude product was recrystallized from EtOH to give 8.54 g (84%) of **9b** as yellow plates: mp 90−91 °C; ^{1}H NMR ($CDCl_3$) δ 9.94 (s, 1H), 7.65−7.55 (m, 5H), 7.33 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 4.23 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.4, 158.2, 154.5, 136.9, 133.6, 130.1, 130.0, 129.2 (2C), 125.2, 116.7, 113.8, 55.1, 32.8; MS (EI) m/z 326 (M^+, 100); IR (KBr) ν 1675, 1524 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.00; H, 4.67; N, 8.54.

5-Chloro-3-(4-chlorobenzyl)-4-formyl-1-phenylpyrazole (9c). Compound **9c** was prepared as for **9a** above employing 3-(4-chlorobenzyl)-1-phenyl-5-pyrazolone (**8c**) (5.7 g, 0.020 mol). The pale brown solid isolated was pure by NMR and TLC for further reaction: yield 5.8 g (88%); mp 87−88 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H), 7.60−7.45 (m, 5H), 7.33 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H), 4.25 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 183.4, 153.5, 136.8, 136.4, 133.9, 132.3, 130.4, 129.2 (2C), 128.4, 125.1, 116.7, 33.1; MS (EI) m/z 330 (M^+, 100); IR (KBr) ν 1681, 1524 cm^{-1}. Anal. Calcd for $C_{17}H_{12}Cl_2N_2O$: C, 61.56; H, 3.65; N, 8.46. Found: C, 61.83; H, 3.74; N, 8.36.

5-Azido-3-benzyl-4-formyl-1-phenylpyrazole (1a). The appropriate 3-benzyl-5-chloro-4-formyl-1-phenylpyrazole (**9a**) (1.48 g, 5 mmol) was dissolved in DMSO (25 mL) in a 100 mL round-bottomed flask, and sodium azide (0.975 g, 15 mmol) was added. The reaction mixture was stirred for 3 d at 35 °C in the absence of light, after which it was diluted with H_2O (200 mL) and extracted with Et_2O (150 mL). The organic phase was washed with brine (3 × 100 mL) and H_2O (150 mL), after which it was dried (Na_2SO_4). Removal of the solvent left a solid residue, which was purified by column chromatography (silica gel, CH_2Cl_2, R_f = 0.46) to give 0.70 g (46%) of **1a** as a green crystalline solid: mp 98−99 °C; ^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1H), 7.80−7.2 (m, 10H), 4.25 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 183.6, 154.4, 140.7, 138.0, 137.0, 129.0, 128.7, 128.5, 126.7, 124.3, 111.8, 33.7; MS (EI) m/z 303 (M^+, 1), 275 ($M^+ - N_2$, 15); IR (KBr) ν 2145, 1669, 1523 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.23; H, 4.28; N, 23.15.

5-Azido-4-formyl-3-(4-methoxybenzyl)-1-phenylpyrazole (1b). Compound **1b** was prepared as for **1a** described above and purified by chromatography (silica gel, CH_2Cl_2, R_f = 0.34) to give 1.47 g (88%) of **1b** as greenish needles: mp 60−61 °C; ^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1H), 7.62 (d br, J = 7.1 Hz, 2H), 7.55−7.4 (m, 3H), 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.18 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.6, 158.4, 154.8, 140.6, 137.0, 130.0, 129.5, 129.0, 128.4, 124.2, 114.1, 111.7, 55.2, 32.8; MS (EI) m/z 333 (M^+, 2), 305 ($M^+ - N_2$, 7); IR (KBr) ν 2147, 1672, 1512 cm^{-1}. Anal. Calcd for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.41; H, 4.46; N, 20.84.

5-Azido-4-formyl-3-(4-chlorobenzyl)-1-phenylpyrazole (1c). Compound **1c** was prepared as above for **1a** and purified by chromatography (silica gel, CH_2Cl_2, R_f = 0.56) to

(22) Interestingly, this procedure appears to produce the keto form exclusively, as opposed to a similar procedure that produces a mixture of the keto an enol forms: Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932−7936.

give 1.07 g (63%) of **1c** as an orange crystalline solid: mp 93−94 °C; ^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1H), 7.7−7.2 (m, 9H), 4.20 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 183.1, 153.8, 140.8, 136.9, 136.4, 132.6, 129.9, 129.1, 128.8, 128.6, 124.2, 111.7, 33.0; MS (EI) *m*/*z* 337 (M^+, 4), 309 ($M^+ - N_2$, 15); IR (KBr) ν 2146, 1672, 1525 cm^{-1}. Anal. Calcd for $C_{17}H_{12}ClN_5O$: C, 60.45; H, 3.58; N, 20.73. Found: C, 60.53; H, 3.62; N, 20.64.

Thermolyses of 5-Azido-4-formylpyrazoles. The appropriate azidopyrazole (1 mmol) was dissolved in toluene (40 mL) in an atmosphere of dry N_2 and stirred at 95 °C while continuously being monitored by TLC (eluent CH_2Cl_2) to reveal two major products. After 4 h, the starting material had been consumed, the reaction mixture was cooled to room temperature, and the toluene was removed in vacuo. The resulting orange solid was chromatographed to give two major fractions; thus, **1a** gave **2a** and **3a**, **1b** gave **2b** and **3b**, and **1c** gave **2c** and **3c**.

4-Cyano-2-phenyl-3-phenylazofuran (2a): yield 77 mg (28%); R_f = 0.57 (CH_2Cl_2), chromatographed on SiO_2 (CH_2Cl_2/cyclohexane 1:1); mp 152−153 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (dd, J = 1.7, 8.2 Hz, 2H), 7.95 (s, 1H), 7.95 (dd, J = 1.6, 8.1 Hz, 2H), 7.6−7.4 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 154.1, 152.3, 150.4, 136.4, 131.6, 130.0, 129.1, 128.8, 128.2, 127.3, 123.0, 112.5, 92.4; MS (EI) *m*/*z* 273 (M^+, 98); IR (KBr) ν 2232 cm^{-1}. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.45; H, 4.09; N, 15.18.

4-Cyano-2-(4-methoxyphenyl)-3-(phenylazo)furan (2b): yield 82 mg (27%); R_f = 0.49 (CH_2Cl_2), chromatographed on SiO_2 (CH_2Cl_2/cyclohexane 1:1); mp 179−180 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 8.9 Hz, 2H), 7.91 (dd, J = 1.6 and 8.0 Hz, 2H), 7.88 (s, 1H), 7.55−7.45 (m, 3H), 7.00 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.1, 154.4, 152.3, 149.9, 135.1, 131.3, 129.1, 128.9, 122.9, 120.9, 114.4, 112.7, 92.3, 55.3; MS (EI) *m*/*z* 303 (M^+, 75); IR (KBr) ν 2236 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 70.89; H, 4.43; N, 13.75. Single crystals for X-ray diffraction were prepared by recrystallization from 1,2-dichloroethane/MeOH.

2-(4-Chlorophenyl)-4-cyano-3-(phenylazo)furan (2c): yield 80 mg (25%); R_f = 0.56 (CH_2Cl_2), chromatographed on SiO_2 (CH_2Cl_2/cyclohexane 2:1); mp 174−176 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (dt, J = 2.1, 8.8 Hz, 2H), 7.95 (s, 1H), 7.94−7.88 (m, 2H), 7.57−7.49 (m, 3H), 7.47 (dt, J = 2.1 and 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 152.9, 152.1, 150.4, 136.5, 136.3, 131.9, 129.2 (2C), 128.3, 126.6, 123.0, 112.3, 92.6; MS (EI) *m*/*z* 307 (M^+, 19); IR (KBr) ν 2239 cm^{-1}. Anal. Calcd for $C_{17}H_{10}ClN_3O$: C, 66.35; H, 3.28; N, 13.65. Found: C, 66.05; H, 3.27; N, 13.71.

3-Benzyl-4-cyano-1-phenylpyrazole (3a): yield 77 mg (30%); R_f = 0.41 (CH_2Cl_2), chromatographed on SiO_2 (CH_2Cl_2/cyclohexane 1:1); mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.70−7.20 (m, 10H), 4.17 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 156.0, 138.7, 137.4, 132.3, 129.6, 128.8, 128.6, 127.9, 126.8, 119.6, 113.2, 93.7, 33.6; MS (EI) *m*/*z* 259 (M^+, 100); IR (KBr) ν 2227 cm^{-1}; HRMS found 259.1104, calcd 259.1110. Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.35; H, 5.15; N, 16.06.

4-Cyano-3-(4-methoxyphenyl)-1-phenylpyrazole (3b): yield 66 mg (23%): R_f = 0.23 (CH_2Cl_2), chromatographed on SiO_2 (CH_2Cl_2); mp 75 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 7.7 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H), 6.86 (dt, 2.0, 8.7, 2H), 4.10 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.4, 156.4, 138.8, 132.3, 129.8, 129.6, 129.4, 127.8, 119.6, 114.0, 113.2, 93.5, 55.2, 32.8; MS (EI) *m*/*z* 289 (M^+, 100); IR (KBr) ν 2230 cm^{-1}; HRMS found 289.1217, calcd 289.1210. Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 75.01; H, 5.22; N, 14.67. Single crystals for X-ray diffraction were prepared by slow evaporation of a solution of **3b** in 10% methanolic HCl.

3-(4-Chlorophenyl)-4-cyano-1-phenylpyrazole (3c): yield 80 mg (25%); R_f = 0.47 (CH_2Cl_2), chromatographed on SiO_2 (CH_2Cl_2/cyclohexane 2:1); mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.64 (dt, J = 1.4, 8.0 Hz, 2H), 7.48 (t, J = 7.2 Hz, 2H), 7.44−7.27 (m, 5H), 4.13 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.5, 138.7, 135.8, 132.7, 132.4, 130.2, 129.7, 128.7, 128.0, 119.6, 113.0, 93.6, 32.9; MS (EI) *m*/*z* 293 (M^+, 100); IR (KBr) ν 2228 cm^{-1}; HRMS found 293.0728, calcd 293.0720. Anal. Calcd for $C_{17}H_{12}ClN_3$: C, 69.51; H, 4.12; N, 14.30. Found: C, 69.43; H, 4.16; N, 14.20.

Azide Thermolysis Optimized for the Production of 4-Cyano-2-(4-methoxyphenyl)-3-(phenylazo)furan (2b). A solution of a mixture of 5-azido-4-formyl-3-(4-methoxybenzyl)-1-phenylpyrazole (**1b**) (300 mg, 0.90 mmol) and 2,3-dichloro-5,6-dicyano-1,4-quinone (**10**) (306 mg, 1.35 mmol, 1.5 molar equiv) in dry toluene (20 mL) was heated at 95 °C in an atmosphere of dry N_2. During this time, the progress of the reaction was monitored by TLC, revealing the gradual appearance of the spot corresponding to the presence of furan **2b**, and at the same time confirming the formation of only trace amounts of the pyrazole **3b**. After 4 h of heating, the reaction was cooled to room temperature, and the solvent was removed in vacuo, leaving a solid residue, which was purified by column chromatography on silica gel (eluent DCM) to give 134 mg of 4-cyano-2-(4-methoxyphenyl)-3-phenylazofuran (**2b**) (0.44 mmol, 49%). This material was identical to the material isolated in the unbiased reaction as described above.

Azide Thermolysis Optimized for the Production of 4-Cyano-3-(4-methoxyphenyl)-1-phenylpyrazole (3b). 5-Azido-4-formyl-3-(4-methoxybenzyl)-1-phenylpyrazole (**1b**) (150 mg, 0.45 mmol) was dissolved in dry toluene (20 mL) under a blanket of N_2, and a mixture of 1,2-diphenylhydrazine (0.68 mmol) and *p*-toluenesulfonic acid (4 mg) was added. The resulting yellow mixture was heated at 95 °C for 4 h while being constantly monitored by TLC as described in the procedure above, after which the solvent was removed in vacuo. The red residue was subjected to column chromatography on silica gel to give, in order of elution, 12 mg of 4-cyano-2-(4-methoxyphenyl)-3-phenylazofuran (**2b**) (0.04 mmol, 9%) and 53 mg of 4-cyano-3-(4-methoxyphenyl)-1-phenylpyrazole (**3b**) (0.183 mmol, 41%). The compound isolated in this experiment were indistinguishable from the products isolated from the thermolysis of 5-azido-4-formyl-3-(4-methoxybenzyl)-1-phenylpyrazole (**1b**).

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1a**−**c**, **2a**−**c**, and **3a**−**c**; crystal data, data collection details and refinement parameters, as well as ORTEP representations of the X-ray crystal structures of **2b** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9822075