JOC Article

Investigations of a Novel Process to the Framework of Benzo[*c*]cinnoline

Hans-René Bjørsvik,* Raquel Rodríguez González, and Lucia Liguori

Department of Chemistry, University of Bergen, Allégaten 41, N-5007 Bergen, Norway

hans.bjorsvik@kj.uib.no

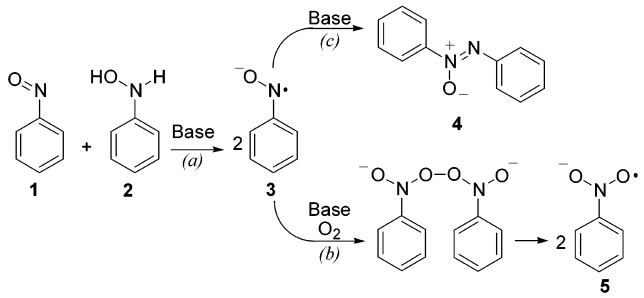
Received May 28, 2004

A novel synthetic process leading to the framework of benzo[*c*]cinnoline has been discovered and investigated. The process is composed of two separate reactions, the first of which is a partial reduction of the nitro groups of the 2,2′-dinitrobiphenyl, a process that we believe proceeds via a SET mechanism to yield the hydroxyamino and nitroso groups. In the following step the cyclization takes place under formation of the −N═N− bond. We believe that this process take place via a radical mechanism through the nitroso radical anion. The novel process affords either benzo[*c*]-cinnoline or benzo[*c*]cinnoline *N*-oxide, both in high yields, 93% and 91%, respectively. To obtain benzo[*c*]cinnoline, the reaction is conducted with an alcohol as solvent and an alkoxide as the base, while for benzo[*c*]cinnoline *N*-oxide, water is used as solvent with sodium hydroxide as the base. To establish the latter procedure, statistical experimental design and multivariate modeling were utilized to reveal the response surface for the reaction and to determine the optimal conditions for the reaction. A proposal for the complex reaction mechanism is given. During the corroboration of the mechanism, a new deoxygenation reaction for converting benzo[*c*]cinnoline *N*-oxide into benzo-[*c*]cinnoline was discovered. The reaction is conducted by treating the *N*-oxide with sodium ethoxide at elevated temperature to achieve near-quantitative conversion into benzo[*c*]cinnoline in a yield of 96%.

Introduction

We have recently reported a new catalytic oxidation process that makes use of nitroarenes as catalysts in aerobic oxidation.[1,2] This catalytic process was derived on the basis of a process where we used the nitroarenes as stoichiometric oxidants.[3] These two processes are both suitable for the oxidation of aromatic compounds containing oxygen-functionalized benzylic carbons. Investigation of the process revealed the involvement of single-electron-transfer (SET) processes. Moreover, during this study a reaction manifold was found that we initially believed to be appropriate for the synthesis of diazenes but found in practice that which it could not be used in this way, it was suitable for the synthesis of *N*-heteroarenes containing the C−N═N−C moiety. The present report will reveal our finding utilizing the reaction manifold for a process leading to the framework of benzo[*c*]cinnoline which provides an interesting class of compounds due to a variety of biological activities, for example, topoisomerase I inhibitors[4] and compounds with fungicidal effects.[5]

SCHEME 1



Methods and Results

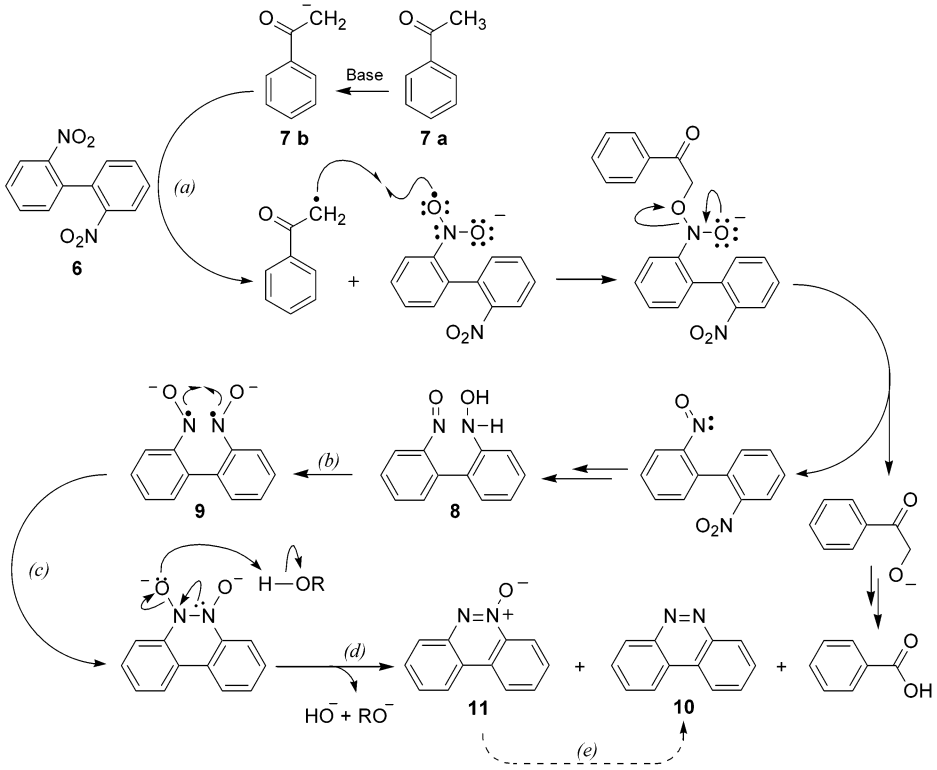
Several years ago, Russell and co-workers[6−8] demonstrated by means of ESR spectroscopy that nitrosobenzene **1** and hydroxyaminobenzene **2** mixed in basic medium react spontaneously to afford two entities of nitrosobenzene anion radicals **3**, pathway (a) of Scheme 1. When the reaction was performed with oxygen present, the nitrobenzene radical anion **5** was observed,[8] as in pathway (b). On the other hand, if the base treatment of **1** and **2** was performed without oxygen present, *N*,*N*′-

* To whom correspondence should be addressed. Phone: +47 55 58 34 52. Fax: +47 55 58 34 52.

(1) Bjørsvik, H.-R.; Liguori, L.; Merinero, J. A. V. *Tetrahedron Lett.* **2002**, *43*, 4985−4987.
(2) Bjørsvik, H.-R.; Liguori, L.; Merinero, J. A. V. *J. Org. Chem.* **2002**, *67*, 7493−7500.
(3) Bjørsvik, H. R.; Liguori, L.; Minisci, F. *Org. Process. Devel. Res.* **2001**, *5*, 136
(4) Singh, S. K.; Yu, Y.; Ruchelman, A.; Sim, S.-P.; Liu, A.; Leroy, F.; LaVoie, E. J. *Abstract of Papers*; 222nd ACS National Meeting, Chicago, August 26−30, 2001; American Chemical Society: Washington, DC, 2001.
(5) Weaver, L. J. (Monsanto Chemical Co.). US Patent 3012909, 1959.
(6) Russell, G. A.; Geels, E. J. *J. Am. Chem. Soc.* **1965**, *87*, 122.
(7) Geels, E. J.; Konaka, R.; Russell, G. A. *Chem. Commun.* **1965**, 13.
(8) Russell, G. A.; Geels, E. J.; Smentowski, F. J.; Chang, K.-Y.; Reynolds, J.; Kaupp, G. *J. Am. Chem. Soc.* **1967**, *89*, 3821.

10.1021/jo049102o CCC: $27.50
Published on Web 10/07/2004

SCHEME 2



diphenyldiazene *N*-oxide **4** was obtained via a coupling of the nitroso radical anion **3**, pathway (c). We have from our laboratory recently disclosed a new catalytic aerobic oxidation[1,2] process based on these early discoveries and our more recently disclosed stoichiometric alkaline nitroarene oxidation method.[3] Our recently unveiled aerobic oxidation process used highly electron-deficient nitroarenes as catalysts in our endeavors to oxidize various aromatics with oxygen-functionalized benzylic carbon to obtain the corresponding carboxylic acids. Here, we will present our findings using oxygen free reaction environments, conditions that should favor the creation of the −N═N− bond, path (c) of Scheme 1, which also constitutes the complementary mechanism for our stoichiometric oxidation process.[3]

The C−N═N−C bond formation step is carried out by reacting the 2,2′-dinitrobiphenyl **6** with acetophenone **7** in basic solution. Under such reaction conditions, 2,2′-dinitrobiphenyl **6** operates as the oxidant for the acetopheneone in a way similar to that as recently described by us.[2] Scheme 2 shows a proposal for this process creation of the C−N═N−C moiety in the current context.

The nitrogroups can be reduced stepwise to the amino group, a process that takes place over three steps, $-NO_2 \rightarrow -N{=}O \rightarrow -NHOH \rightarrow -NH_2$. Under the reductive conditions for the nitro groups of 2,2′-dinitrobiphenyl **6**, the partially reduced product *N*-(2′-nitrosobiphenyl-2-yl)-hydroxylamine **8** will be formed during the course of the redox process. The nitroso and hydroxylamine groups of this intermediate react spontaneously[8] to form two entities of nitroso radical anion (similar to pathway (a) of Scheme 1). However, in the present case, the process proceeds via an intramolecular SET mechanism to provide 2,2′-dinitrosoyl radical anion-biphenyl **9**, pathway (b) of Scheme 2. Under suitable reaction conditions, the 2,2′-dinitrosoyl radical anion-biphenyl **9** cyclizes to afford benzo[*c*]cinnoline **10** or the less reduced compound benzo-[*c*]cinnoline *N*-oxide **11**, pathway (c) → (d) of Scheme 2: this represents an complementary pathway to our aerobic oxidation process.[1,2]

In our endeavor to accomplish the synthetic process as outlined in Scheme 2, investigations were performed along two different lines, namely (i) by using conditions such as revealed for the stoichiometric alkaline nitroarene oxidation[3] that is performed in aqueous sodium hydroxide (40%) and (ii) by using an organic solvent with an alkoxide as base. We believed that both of these redox processes involve a "cage re-bonding" step. Such reaction mechanisms are usually very dependent on the solvent properties, especially the solvent viscosity, and thereby the reaction temperature. A variety of solvents and bases were thus investigated. The results of this screening are portrayed in Scheme 3. It is clearly evident from these data that the success of the process depends on both the type of reaction medium and the type of base that is utilized. Interestingly, some of the solvent and base combinations afford both the benzo[*c*]cinnoline and the benzo[*c*]cinnoline *N*-oxide (entries 1, 3, 4, 6, and 7). When the solvent/base combinations EtOH/EtONa (entry 5), *i*-PrOH/*i*-PrONa (entry 8), or PrOH/PrONa (entry 9) are used, benzo[*c*]cinnoline **10** is obtained with excellent yield to the exclusion of the *N*-oxide.

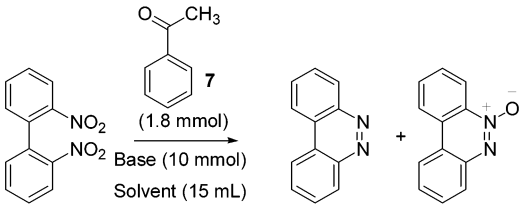
The proposed reaction mechanism given in Scheme 2 was assembled as a complementary pathway based on previously disclosed studies.[3−8] The mechanism describes the reduction and cyclization process leading to benzo-[*c*]cinnoline *N*-oxide **11**. However, the last reduction step, namely the conversion of benzo[*c*]cinnoline *N*-oxide **11** into benzo[*c*]cinnoline **10,** could not be accounted for on the basis of previous experiments. In an attempt to

TABLE 1. Experimental Design with Adjacent Measured Responses

	experimental variables[a]				responses[c]		
no.	x_1	x_2	x_3	x_4[b]	y_6	y_{10}	y_{11}
1	1.8	15.0	140	3.0	87.64	1.68	3.45
2	2.2	15.0	140	5.0	37.01	5.45	57.92
3	1.8	25.0	140	5.0	50.32	6.25	45.75
4	2.2	25.0	140	3.0	57.94	11.01	35.28
5	1.8	15.0	160	5.0	42.70	4.67	42.28
6	2.2	15.0	160	3.0	22.13	4.25	56.09
7	1.8	25.0	160	3.0	55.00	5.07	45.17
8	2.2	25.0	160	5.0	14.74	5.02	70.85
9	2.0	20.0	150	4.0	49.74	4.75	48.07
10	1.6	20.0	150	4.0	55.04	4.11	36.80
11	2.4	20.0	150	4.0	20.04	5.35	61.95
12	2.0	10.0	150	4.0	38.72	4.82	54.19
13	2.0	30.0	150	4.0	34.12	4.03	59.19
14	2.0	20.0	130	4.0	94.22	0.00	0.00
15	2.0	20.0	170	4.0	25.12	4.95	57.10
16	2.0	20.0	150	2.0	43.17	7.21	44.80
17	2.0	20.0	150	6.0	38.39	3.74	50.03
18	2.4	25.0	157	4.5	11.00	5.01	78.87
19	3.0	25.0	157	4.5	2.71	9.49	90.71
20	2.4	30.0	167	2.0	34.91	5.41	71.60
21	3.4	30.0	167	2.0	0.00	9.49	86.47

[a] Procedure: 2,2'-dinitrobiphenyl **6** (2.06 mmol, 0.503 g) was added to a solution of NaOH and acetophenone **7**. Experimental variables: x_k (definition), levels [−2, −1, 0, +1, +2]/unit; x_1, (amount of acetophenone) [1.6, 1.8, 2.0, 2.2, 2.4]/mmol; x_2, volume of NaOH (40%) [10, 15, 20, 25, 30]/mL; x_3, reaction temperature [130, 140, 150, 160, 170]/°C; x_4, reaction time [2, 3, 4, 5, 6]/*h*. [b] Generator for the 2^{4-1} design: $x_4 = x_1 \times x_2 \times x_3$ (used to decide the settings for experimental variable x_4 based on the settings of the three other experimental variables x_1−x_3). [c] The measured responses are as follows: y_6, 2,2′-dinitrobenzene/recovered (%); y_{10}, benzo[*c*]cinnoline/yield (%); y_{11}, benzo[*c*]cinnoline *N*-oxide/yield (%). The % values are all calculated on the basis of the initial quantity of 2,2′-dinitrobiphenyl.

SCHEME 3



#	Base	Solvent	**10**	**11**
1	*tert*-BuOK	*tert*-BuOH	42	35
2	*tert*-BuOK	$PhCF_3$	77	-
3	MeONa	MeOH	14	40
4	MeONa	$PhCF_3$	16	22
5	EtONa	EtOH	91	-
6	EtONa	$PhCF_3$	68	23
7	NaOH(40%)	H_2O	24	57
8	*iso*-PrONa	*iso*-PrOH	93[a]	-
9	PrONa	PrOH	93[a]	2
10[b]	*iso*-PrONa	$(CF_3)_2CHOH$	-	-
11	NaOH	EtOH	96	-

[a] Mean value of two experiments

[b] 97% of the starting material was recovered (isolated)

establish if an additional final step **11** → **10**, path (e), operated during the influence of the alkoxides, a sample of benzo[*c*]cinnoline *N*-oxide **11** was treated with sodium ethoxide in ethanol under similar conditions as for the process to benzo[*c*]cinnoline **10** as described above, Scheme 4. In essence, a quantitative conversion of the *N*-oxide **11** to the deoxygenated compound **10** was achieved. Additional experiments at three different reaction times, namely at 30, 90, and 140 min, were performed. The sample contained initially approximately 87% of **11** and 13% of **10**. The final time−concentration profiles for the two compounds **10** and **11** are shown on the right-hand side of Scheme 4. This plot reveals that the conversion is completed after a reaction time of 140 min. A vertical parallel displacement of the conversion curve (that thus initiates in 100%) reveals that an additional ∼40 min is required for conversion of a pure sample of benzo[*c*]cinnoline *N*-oxide; see the dashed curve in Scheme 4. An additional experiment performed using sodium hydroxide as base and ethanol as solvent revealed a complete conversion of with excellent yield (>96%).

The experiment reported in entry 7 of Scheme 3 using sodium hydroxide as base and water as the reaction medium attracted our attention as a potential method for the synthesis of the benzo[*c*]cinnoline *N*-oxide **11**. On the basis of this experiment, an experimental design suitable for response surface modeling was laid out; see entries 1−17 of Table 1. Adjacent to the experimental conditions (x_1, ..., x_4) are shown the responses: % nonconverted 2,2′-dinitrobiphenyl (y_6), percent yields of benzo[*c*]cinnoline (y_{10}), and percent yields of benzo[*c*]cinnoline *N*-oxide (y_{11}), respectively.

The experimental variables of the design setup viewed in Table 1 were scaled according to eq 1 in order to facilitate the estimation of the regression coefficients, the β's, of eq 2.

$$x_i = \frac{z_i - \left\{z_{i,\mathrm{L}} + \frac{1}{2} \times (z_{i,\mathrm{H}} - z_{i,\mathrm{L}})\right\}}{z_{i,\mathrm{H}} - \left\{z_{i,\mathrm{L}} + \frac{1}{2} \times (z_{i,\mathrm{H}} - z_{i,\mathrm{L}})\right\}}, \; i = 1, ..., 4 \quad (1)$$

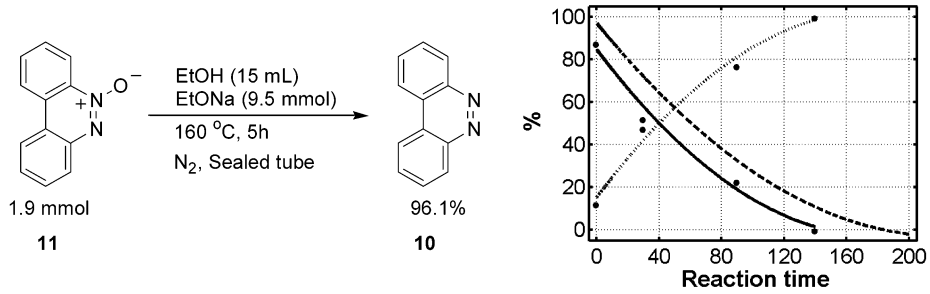
x_i of eq 1 is the experimental variable i given in scaled units, z_i is the experimental variable i given in real units, and $z_{i,\mathrm{L}}$ and $z_{i,\mathrm{H}}$ are the selected low (−1) and high (+1) experimental values (real unit), respectively, of the experimental variable i. The model matrix was created by including the design matrix after a column of ones, the two-variable interactions ($x_i \times x_j$), and the quadratic terms (x_i^2) of each of the four experimental variables x_i, $i = 1, ..., 4$. The final model matrix in scaled values (17 lines × 15 columns) with their corresponding yield values y_{11} of target molecule benzo[*c*]cinnoline *N*-oxide was then submitted to multivariate modeling in terms of the multiple linear regression method (MLR)[9] and the partial least squares regression (PLSR) method[10] to provide an empirical model as depicted in eq 2.

$$\hat{y}_{11} = \hat{\beta}_0 + \sum_{i=1}^{I} \hat{\beta}_i x_i + \sum \sum_{i<j}^{I} \hat{\beta}_{ij} x_i x_j + \sum_{i=1}^{I} \hat{\beta}_i x_i^2, \; i = 1, ..., 4 \quad (2)$$

(9) See, for example: (a) Draper, N. R.; Smith, H. *Applied Regression Analysis*, 3rd ed.; Wiley: New York, 1998. (b) Montgomery, D. C.; Peck, E. A. *Introduction to linear regression analysis*; Wiley: New York, 1982.

(10) Malinowski, E. R. *Factor analysis in chemistry*, 3rd ed.; Wiley: New York, 2002.

SCHEME 4



The final empirical mathematical predictive model for the response yield (%) of benzo[*c*]cinnoline *N*-oxide **11** (y_{11}) is shown in eq 3.

$$\hat{y}_{11} = 47.9635 + 8.3630x_1 + 2.9557x_2 + 11.6359x_3 + 5.4544x_4 - 6.6337x_3 \times x_4 + 2.0657{x_2}^2 - 4.9691{x_3}^2 \quad (3)$$

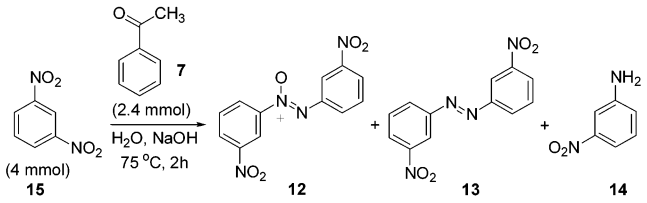
This model was developed with the PLSR method using $a = 4$ PLS components. The product statistics indicates a fairly good model; ${R_{11}}^2 = 0.909$, ${Q_{11}}^2 = 0.627$, $\mathrm{RMSEP}_{11} = 5.489$, and $\mathrm{RSD}_{11} = 5.844$.

The model of eq 3 was used to estimate response surfaces projected as iso-contour maps, shown in Figure 1. A straightforward interpretation of this response surface reveals that it is compulsory to apply a rather high reaction temperature, concomitant with large quantities of sodium hydroxide (large volume) and acetophenone, and a medium-long reaction time (4.5−5 h). Such conditions are found in the sub iso-contour map located in the upper right corner of Figure 1. However, during the investigation of the reaction leading to benzo[*c*]cinnoline *N*-oxide **11**, it was observed that high reaction temperatures (>170 °C) were detrimental to the process, most probably due to concurrent or subsequent degradation reactions. Reaction temperatures below <140 °C resulted in very low conversion and yield. By means of the iso-contour projections of the response surface (Figure 1) and these additional constraints, the experimental conditions for some few optimizing experiments with the goal of evaluating the predictive capacity of the developed model and finally to determine the optimal conditions for the process were selected and carried out.

Entries 18 and 19 of Table 1 show successfully how the response surface iso-contour projections can operate as a tool for predictive purposes. If the response surface iso-contour projection is interpreted carefully, one can see that by moving horizontally to the right on the outer abscissa axis (variable x_1) and keeping the other variables constant, an increased yield is predicted. This observation was used to decide the experimental conditions for the trial reported in entry 19, which only represents a small variation of trial 18, augmenting the quantity of acetophenone from 2.4 to 3.0 mmol. These settings however, embody a subresponse surface iso-contour projection that is not included in Figure 1. The anticipated improvement was realized when the experiment was carried out; see entry 19. Similarly, an improvement was also achieved when a reaction was conducted at a shorter reaction time concomitant with an elevated reaction temperature. Motivated by the predictions of the subcontour maps lower right corner−high yield at short reaction time and elevated temperature, the experimental settings of entry 20 of Table 1 was selected. The model predicts a yield of approximately 90%.[11] However, when the experiment was carried out, a yield of approximately 72% was achieved.[12] When the quantity of acetophenone is augmented to 3.4 mmol, keeping the other experimental variables at the same levels as in experiment 20, a yield of approximately 86% is achieved. Again the tendencies depicted in the contour map were successfully applied to predict a high yielding synthetic procedure, even if the required settings represent long-range extrapolation.

Attempts To Synthesize Diphenyldiazenes. The two synthetic methods for the preparation of benzo[*c*]cinnoline **10** and benzo[*c*]cinnoline *N*-oxide **11**, respectively, were used in attempts to prepare diphenyldiazene derivatives **12** and **13** of Scheme 5. The experiments were

SCHEME 5



carried out at two different temperatures, namely at 75 and 157 °C, and conducted for 2 and 5 h with 1,3-dinitrobenzene **15** as the substrate. Furthermore, two solvent and base systems, (i) water and sodium hydroxide, and (ii) *i*-PrOH and *i*-PrONa, were used in the trials.

GC−MS analysis of isolated raw products were compared with previous experimental results.[13,14] These analyses revealed that the reaction that was carried out in water, with NaOH as base, at 75 °C contained the expected product *N*,*N*′-bis(3-nitrophenyl)diazene *N*-oxide **12** (16%), minor amounts of bis(3-nitrophenyl)diazene **13** (3%), and the reduction product 3-nitrophenylamine **14** (25%). When the reaction was conducted at 75 °C with

(11) The prediction is performed by using the following conditions: $x_1 = 2.4$ mmol, $x_2 = 30$ mL, $x_3 = 167$ °C, and $x_4 = 2$ h. This position is found in the subplot in the upper-right corner of Figure 1. The lower right corner of this subplot predicts 90% yield.

(12) The developed model predicts an "optimized" yield at the settings of short reaction time and elevated reaction temperature. Most probably this is due to a model error that becomes visible when "long-range" extrapolation is performed. In fact, only one experiment has previously been performed at such a short reaction time and included in the training set (entry 16 of Table 1) for the predictive model eq 3.

(13) El'tsov A. V.; Kuznetsova N. A.; Frolov A. N. *Zh. Org. Khim.* **1971**, *7* (4), 817−820.

(14) Khan M. S.; Lone A.; Kashmiri M. A. *J. Nat. Sci. Math.* **1990**, *30* (2), 77−81.

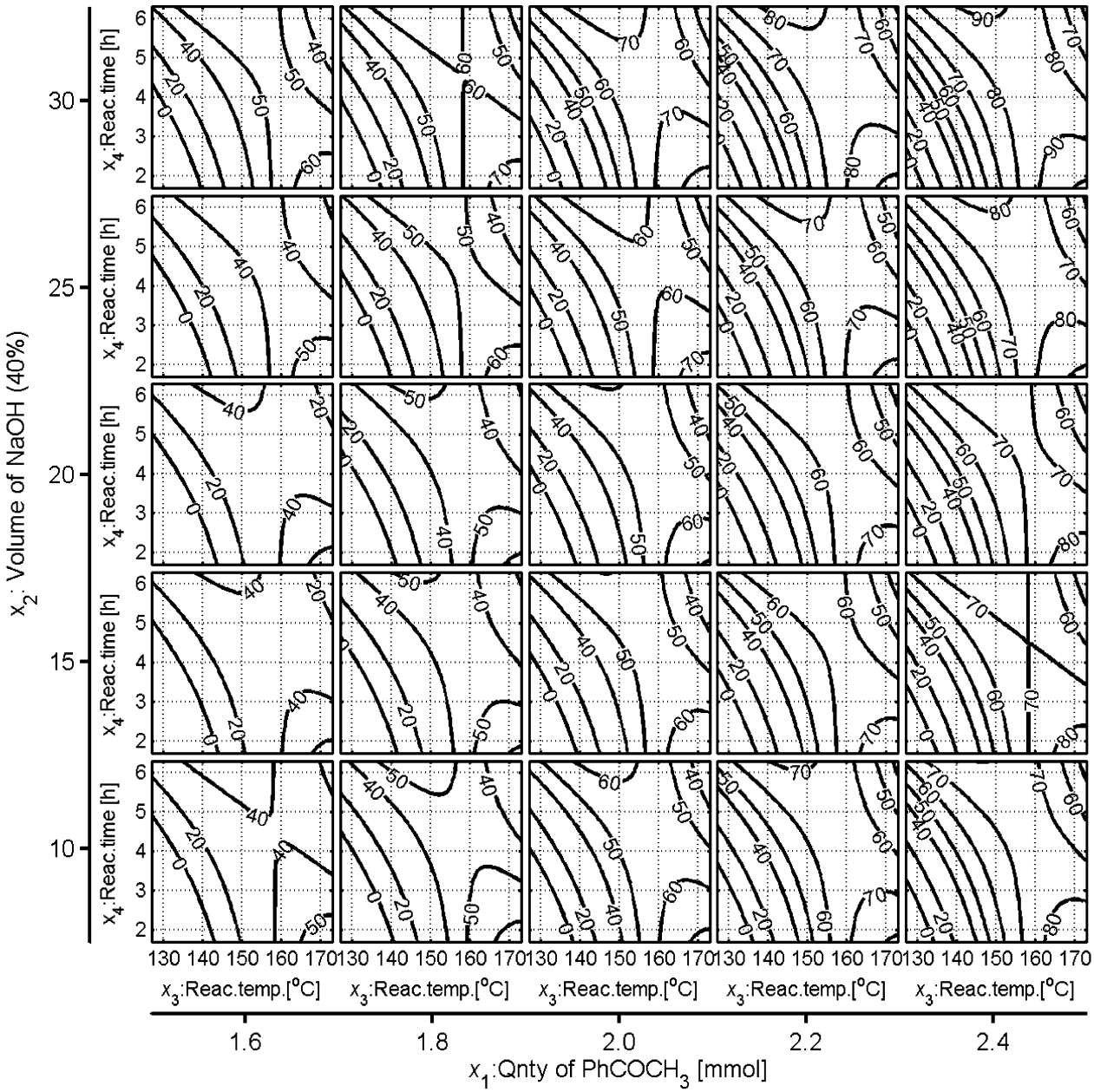


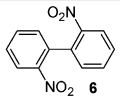
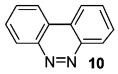
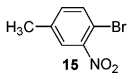
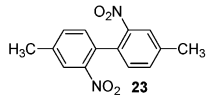
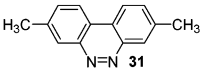
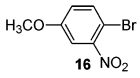
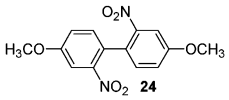
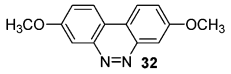
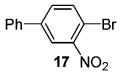
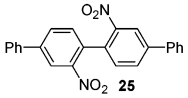
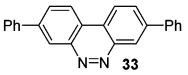
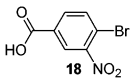
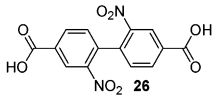
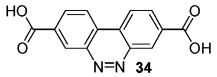
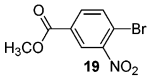
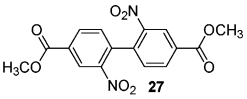
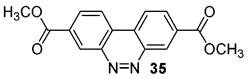
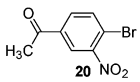
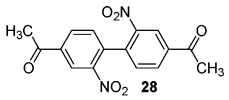
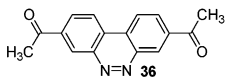
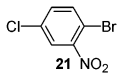
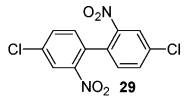
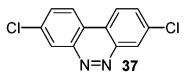
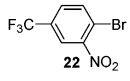
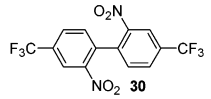
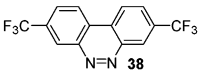
FIGURE 1. Multidimensional contour plot showing the predicted yield as a function of four experimental variables: quantity of acetophenone [mmol] (x_1), volume of NaOH (40%) solution [mL] (x_2), the reaction temperature [°C] (x_3), and the reaction time [h] (x_4). Multidimensional response surface plots in terms of contour plots describe variation in one or more responses that is given by the contour lines and two or more experimental variables. In the present plot, the contour lines show the yield of target molecule benzo[*c*]cinnoline *N*-oxide when the four experimental variables x_1-x_4 are varied. The experimental variables x_3 and x_4 are varied continuously in the ranges of 130−170 °C and 2−6 h, respectively. The two variables x_1 and x_2 are both varied on five discrete experimental levels each that are [1.6, 1.8, 2.0, 2.2, 2.4]/mmol and [10, 15, 20, 25, 30]/mL, respectively.

2-propanol and sodium isopropoxide as solvent and base, respectively, the only product observed in substantial quantity was 3-nitrophenylamine **14** (27%). Minor quantities (<3%) of the benzene-1,3-diamine were also detected. The corresponding reactions performed at the elevated temperature (157 °C) resulted in each case only in degradation products and a low yield of the diazene products; this supports our proposed mechanism involving a "cage re-bonding" step. Such a mechanism disfavors, of course, the combination of two separate molecular entities as in Scheme 5. Moreover, several other reactive species (Scheme 2) that are present during the redox process will compete for the 3-nitronitrosyl radical anion species when liberated from the solvent cage.

Attempt To Synthesize Various Substituted Benzo[*c*]cinnolines. To validate the generality of our new process to the framework of benzo[*c*]cinnoline, a series of various substituted 2,2′-dinitrobiphenyls (**23**−**30**) were subjected to the conditions of the optimized reaction conditions. The series of 2,2′-dinitrobiphenyls **23**−**30** shown in Table 2 were prepared utilizing the Ullmann coupling reaction[15−17] with 2-nitrobromoben-

(15) Ullmann, F. *Ann.* **1904**, *332*, 38.

TABLE 2. Various 2,2′-Dinitrobiphenyl Derivatives Submitted for the Novel Process[a] to the Benzo[*c*]cinnoline Framework

#	1-Bromo-2-nitro-benzene	2,2'-Dinitrobiphenyl	Yield	Benzo[*c*]cinnoline	Yield
1	–	 **6**	–	 **10**	94
2	 **15**	 **23**	99	 **31**	96
3	 **16**	 **24**	96	 **32**	85
4	 **17**	 **25**	19	 **33**	95
5	 **18**	 **26**	26	 **34**	9
6[c]	 **19**	 **27**	7	 **35**	~50
7[a,b]	 **20**	 **28**	48	 **36**	–
8[c]	 **21**	 **29**	58	 **37**	~50
9	 **22**	 **30**	97	 **38**	90

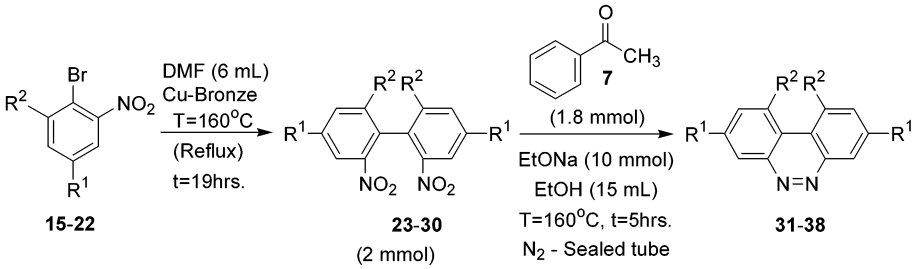
[a] **2,2′-Dinitrobiphenyl Derivatives.** To a solution of the 1-bromo-2-nitrobenzene in DMF was added Cu−Bronze (in two portions, adding the second after 4 h of reaction time). The mixture was heated at 160 °C for 19 h with reflux, at atmospheric pressure. The reaction mixture was then quenched with water. The solid crude product was isolated by filtration. The isolated solid was extracted with MeOH and filtered to remove undissolved inorganics and tars. The solvent was removed under vacuum to obtain the 2,2′-dinitrobiphenyl derivative. **Benzo[*c*]cinnoline derivatives.** 2,2′-Dinitrobiphenyl and acetophenone were added to a basic solution of EtONa (from dissolving Na^0 in EtOH). The resulting solution was placed into a sealed tube under N_2, heated at 160 °C for 5 h, quenched with H_2O (40 mL), and extracted with EtOAc (3 × 40 mL). The major product is the benzo[*c*]cinnoline derivative. [b] In this case, the redox process proceeds intramolecularly by means of three different functional group transformations. [c] The reaction mixture contained several products, the structures of which were not determined. A rough estimate for the yield of target molecule was performed by means of GC−MS.

zenes (**15**−**22**) as the starting materials. The 2,2′-dinitrobiphenyls, were variably functionalized, but $-NH_2$, −OH, and −CN were excluded, since previous experiments under comparable redox conditions revealed a mismatch for those groups. Such groups easily form radicals resulting only in degradation products and tars. Likewise, the functional groups $-COCH_3$, −CHO, and $-CH_2OH$ are not compatible with the reaction conditions because such groups can participate in the redox process ultimately oxidizing them to the carboxylic acid groups. However, in the series of compounds that were submitted to the conditions of the novel process, a compound with the acetyl group was included (entry 7, Table 2). This compound (**28**) was especially interesting, as this molecular entity could tentatively operate both as substrate and reagent in the redox process; however, it failed to react. The other experiments performed included the following functional groups: $-CH_3$, $-OCH_3$, −Ph, −COOH, $-COOCH_3$, −Cl, and $-CF_3$. The conditions utilized and results are summarized in Scheme 6 and Table 2. Except

(16) Ullmann, F.; Sponagel, P. *Ber.* **1905**, *38*, 2211.

(17) See, e.g.: Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's textbook of practical organic chemistry*; Longman Scientific and Technical: Burnt Mill, Harlow, 1978; pp 610−611.

SCHEME 6



for the compound carrying an acetyl group (**28**), it was only the 2,2′-dinitrobiphenyl substituted with the −COOH group (compound **26**) that provided a low yield. The corresponding methylester (**27**) of that compound and 2,2′-dinitrobiphenyl derivative **29** both provided acceptable yields (∼50%). All of the other 2,2′-dinitrobiphenyl derivatives provided excellent yields.

Conclusions

A process leading to benzo[*c*]cinnoline **10** and benzo[*c*]cinnoline *N*-oxide **11** has been discovered and investigated. During the investigation of the process it was discovered that the types of solvent and base were of paramount importance for the course of the process. Likewise, the reaction temperature should carefully be kept within the range 155−167 °C to achieve optimal yields. The quantity of acetophenone, which functions as a reductant, should, when using the process for the preparation of benzo[*c*]cinnoline **10**, be used in slightly less than molar quantities. When synthesizing benzo[*c*]cinnoline *N*-oxide **11** a moderate molar excess of acetophenone is required. When the optimized experimental conditions are used, excellent selectivity and yields are achieved for either of the two products, namely 93% (**10**) and 91% (**11**). The novel process to benzo[*c*]cinnoline can successfully be utilized for the preparation of various substituted benzo[*c*]cinnolines in most cases with medium to high yields, Table 2. As for the previously disclosed catalytic aerobic oxidation process,[1,2] the novel combined redox and cyclization process forming the benzo[*c*]cinnoline framework is not compatible with functional groups such as −CN, $-NH_2$, and −OH, as such groups easily forms free radicals under the redox conditions and result in nonselective processes: these form only degradation products or tars.

We believe that the reaction proceeds by a complex reaction mechanism, some facets of which are outlined in Scheme 3. Likewise, we think that the initial redox process (path (b), Scheme 2) forming the radicals is analogous to the mechanisms we have previously disclosed.[1−3] Additionally, the work of Russell and coworkers[6−,8] described conclusive evidence for the single electron-transfer reduction of nitroarenes in basic media, and for the formation of C-centered radicals and nitroarene radical anions by reactions of carbanions with nitroarenes.

Experiments conducted at (i) prolonged reaction times at low temperatures or (ii) at short reaction times with elevated reaction temperature did not provide high yields as anticipated by the response surface. Explanations for this may be as follows: (i) When the reaction temperature is <140 °C, the redox process did not operate; see, e.g., experiment entry 14. (ii) When elevated temperatures are utilized, high conversions of 2,2′-dinitrobiphenyl **6** are accomplished, but most probably this is due to successive degradation reactions. Moreover, when the process is carried out at reaction temperatures that exceed 170 °C, the solvent cage that encloses the reactive species may be weakened, which results in leakage of the reactive species that can provide other reduction products or tars.

We believe that the disclosed process can find application for synthetic purposes, even if the process requires a slightly elevated temperature to operate satisfactory. The elevated temperature is a minor drawback compared to the advantages of the novel process: (i) the process operates in the absence of any transition (or heavy) metals in catalytic or stoichiometric quantities, (ii) no toxic or hazardous reagents are required, (iii) the process is operated with cheap reagents and solvents, (iv) the novel process provides as high selectivity and yield as the most of the other processes and methods previously disclosed by other researchers,[18−24] and (v) no harmful side products are produced during the process. In all, the disclosed process appears to be an attractive method for benzo[*c*]cinnolins and may thus provide an alternative for industrial applications.

Experimental Section

Benzo[*c*]cinnoline: Workup with Flash Chromatography. The reaction was carried out in a sealed tube reactor of 50 mL capacity. The reaction tube was flushed with nitrogen, and the reactants 2,2′-dinitrobiphenyl (Aldrich 97%) (2.0 mmol, 0.488 g) and acetophenone (1.8 mmol, 0.212 mL) were dissolved in ethanol (15 mL) and placed in the reaction tube. Finally, sodium ethoxide (10 mmol, 0.230 g) was added.

The reaction mixture was heated at 160 °C for 5 h and quenched with water (50 mL) followed by filtration on Celite. The filtrate was extracted with ethyl acetate (3 × 50 mL). The organic phase, which contained the target product, was dried over anhydrous sodium sulfate and filtered and the solvent removed under vacuum to obtain the crude product (564 mg). This material was purified and separated by means of standard flash chromatography[25] using a column of i.d. 3 cm. The eluent was ethyl acetate and *n*-hexane in the ratio 1:4 ($R_{f\,(10)}$ = 0.334, $R_{f(11)}$ = 0.182). The crude material (564 mg) was

(18) Ettienne, A.; Izoret, G. *Bull. Soc. Chim. Fr.* **1964**, 2897.
(19) Everett, J. L.; Ross, W. C. *J. Chem. Soc.* **1949**, 1972.
(20) King, F. E.; King, T. J. *J. Chem. Soc.* **1945**, 824.
(21) Ross, S. D.; Kahn, G. J.; Leach, W. A. *J. Am. Chem. Soc.* **1952**, *74*, 4122.
(22) Laskar, D. D.; Prajapti, D.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 67−69.
(23) Pink, M.; Young, V. G. *J. Org. Chem.* **2000**, *65*, 6388.
(24) Wada, S.; Urano, M.; Suzuki, H. *J. Org. Chem.* **2002**, *67*, 8254−8257.
(25) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

loaded on the column. In total, 150 fractions of 10 mL were collected. Fractions 49−123 were determined to contain pure benzo[*c*]cinnoline (281 mg). The isolated sample of benzo[*c*]-cinnoline was compared with ^{1}H NMR spectra of an authentic sample.[24,26]

Benzo[*c*]cinnoline: Workup with Crystallization. Acetophenone (3.6 mmol, 0.424 mL) and 2,2′-dinitrobiphenyl (4.12 mmol, 1.070 g) were added to a basic solution of sodium ethoxide, obtained from reacting Na-metal (20 mmol, 0.460 g) with ethanol (30 mL). The resulting solution was placed in a sealed tube reactor under nitrogen atmosphere and heated at 160 °C for 5 h. The reaction mixture was then quenched with water (70 mL) followed by filtration on Celite and silica.

The filtrated aqueous solution was extracted with ethyl acetate (3 × 70 mL). The organic phase, which contained the target product, was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under vacuum to obtain the crude product (786 mg). The sample was analyzed on GC utilizing a correction factor to determine the quantity of benzo-[*c*]cinnoline (91% yield, 90% purity). The sample from the flash chromatography was dissolved in refluxing *n*-hexane (70 mL) and filtrated. The resulting yellow solution was allowed to cool on an ice bath for a period of 1 day to achieve yellow crystals (462 mg) of benzo[*c*]cinnoline of a purity of practically 100% measured on GC.

Benzo[*c*]cinnoline *N*-Oxide. To a 40% aqueous solution of NaOH (25 mL) were added acetophenone (0.281 mL, 2.4 mmol) and 2,2′-dinitrobiphenyl (0.503 g, 2.0 mmol). The reaction was carried out at 157 °C (oil bath) with stirring for 4 h 30 min at atmospheric or slightly elevated pressure by means of a sealed tube reactor. After a few minutes of reaction time, the reaction mixture became dark orange, which during the course of the reaction changed to dark brown.

The basic water phase was diluted by adding more water (50−70 mL) and extracted with ethyl acetate (3 × 70 mL). The organic and water phases were passed through a Celite layer in order to remove tars.

The basic water phase was acidified using concentrated HCl (37% solution) until pH 1−2 and then extracted with ethyl acetate (3 × 70 mL). This acidic phase contained pure benzoic acid.

The organic phase contained benzo[*c*]cinnoline, benzo[*c*]-cinnoline *N*-oxide, unreacted 2,2′-dinitrobiphenyl, and acetophenone analyzed by GC−MS to give a preliminary conclusion that benzo[*c*]cinnoline (9%) and benzo[*c*]cinnoline *N*-oxide (90% yield) were the two major products in the final crude (530 mg). The isolated crude product was separated and purified by means of flash chromatography. A column of i.d. 4 cm was used. The eluent was ethyl acetate and *n*-hexane in the ratio 2:3 ($R_{f(\mathbf{10})} = 0.566$, $R_{f(\mathbf{11})} = 0.440$). The total quantity of crude material that was loaded on the column was 864 mg. One hundred and twelve fractions of 10 mL each were collected. Fraction numbers 54−112 were determined to contain pure benzo[*c*]cinnoline *N*-oxide (305 mg). The spectral data obtained for the isolated sample of benzo[*c*]cinnoline *N*-oxide were compared with those of an authentic sample.[26]

***N,N′*-Bis(3-nitrophenyl)diazene *N*-Oxide.** A sealed tube reactor was flushed with nitrogen, and aqueous NaOH (40%, 15 mL), 1,3-dinitrobenzene (0.672 g, 4 mmol), and acetophenone (0.281 mL, 2.4 mmol) were then added.

The reaction mixture was heated at 75 °C (oil bath) with stirring for 2 h. The basic water phase was diluted with water (50 mL), passed through a pad of Celite, and extracted with ethyl acetate (3 × 70 mL). The organic phase was then dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The isolated compound was analyzed via GC−MS, and this showed the presence of *N*,*N*′-bis-(3-nitrophenyl)-diazene *N*-oxide (16%), bis-(3-nitrophenyl)diazene (3%), and 3-nitrophenylamine (25%).

Ullmann Coupling Reaction. To a solution of the 2-nitrobromobenzene (2.0 mmol) in DMF (6.0 mL) was added Cu-bronze in two portions (0.30 g at start of the reaction, then another portion of 0.30 g after 4 h.). The reaction mixture was heated at 160 °C for 19 h with reflux condenser at atmospheric pressure. The final solution was cooled and then quenched in water (60 mL). The solid was filtered off and extracted (3 × 70 mL) with warm methanol (65 °C). The ethanol extracts were combined and filtered, and the solvent was removed under vacuum. The isolated crude contained the Ullmann coupling product as the major product in yields of 19−97%.

Multivariate Calculations and Graphics. Calculations and the graphical representations were performed by means of in-house developed procedures for MATLAB version 6.1.[27]

The MATLAB procedures have previously been validated by comparison of the calculated results with computational results obtained from several commercial computer programs for statistics and mathematical model building.

Acknowledgment. Economic support from the Research Council of Norway is gratefully acknowledged. Professor George Francis is acknowledged for linguistic assistance.

Supporting Information Available: General experimental information and copies of ^{1}H NMR spectra for compounds **10**, **11**, **23**−**25**, **28**−**33**, and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049102O

(26) Kilic, E.; Tüzün, C. *Org. Prep. Proced. Int.* **1990**, *22*, 485−493.

(27) (a) Using Matlab, Version 6, The MathWorks Inc., Natick, MA. (b) Using Matlab Graphics Version 6, The MathWorks Inc., Natick, MA.