Synthesis of Medium- and Large-Size Rings by Intramolecular Nitrile Oxide Dimerization: An Efficient C−C Bond-Forming Ring-Closing Reaction

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The formation of medium- and large-size ring systems remains a permanent challenge for organic chemists as they are widespread, ranging from naturally occurring compounds to macrocyclic synthetic receptors or ligands. The synthesis depends essentially on the intrinsic carbo- or heterocyclic nature of their framework.[1] As for heterocyclic structures, the ring closures are usually performed by carbon−heteroatom bond formation, e.g., ester, amide, or ether bonds. These approaches are well documented, and the procedures are optimized especially for macrocyclic natural products.[2] In contrast, for carbocyclic molecules, particularly for highly functionalized structures, synthesis involving intramolecular carbon−carbon bond formation is often troublesome.

A number of reactions such as Wurtz coupling,[3] alkylation of malonic esters,[4] acyloin condensation,[5] and samarium diiodide-promoted reaction[6] were applied to synthesize carbocyclic skeletons. However, low yields are often obtained for strained medium-ring systems or for highly functionalized structures mainly for compatibility reasons between the reagent and the functional groups present on the molecules.

Recently, the reductive coupling of aldehydes using low-valent titanium,[7] intramolecular olefin metathesis,[8] and other metal-mediated coupling reactions[9] were used as key reactions for the synthesis of complex natural products having highly functionalized carbocyclic backbone. These recent achievements emphasize the synthetic challenge of ring-closing reactions by using mild reaction conditions and reagents compatible with a large panel of functionality.

Herein, we report a C−C bond ring-closing reaction for the synthesis of carbocyclic structures using dialdehydes as starting material. The ring closures proceed via intramolecular dimerization of nitrile oxides resulting in the formation of furoxan moieties that can easily be converted into 1,2-dioximes, 1,2-diketones, 1,2-diols, or 1,2-diamines.[10]

Nitrile oxides are reactive intermediates, generated in situ, and are generally involved in cycloaddition reactions in the presence of various dipolarophiles. Intramolecular nitrile oxide cycloaddition (INOC) has proved to be an efficient method to prepare small and large functionalized carbocycles. This reaction finds interesting synthetic applications but suffers from a few limitations. Under unfavored conditions, e.g., with hindered dipolarophiles or in the absence of dipolarophiles, dimerization of nitrile oxides into furoxan was observed predominantly.[11]

While cycloaddition reactions involving nitrile oxides and dipolarophiles were extensively studied and used in organic synthesis, nitrile oxide dimerization reactions leading to furoxan formation remain a reaction of poor synthetic interests. To our knowledge, intramolecular bis-(nitrile oxide) dimerization has been reported only once by Marx et al. in 1977 for the preparation of a five-membered-ring carbocycle, an intermediate for biotin synthesis.[12] Despite this early result, the potential of this reaction was never exploited to develop a synthetically useful method for the preparation of carbocyclic compounds.

In our initial study, we evaluated the importance of the stability of the nitrile oxide intermediates on the outcome of the intramolecular dimerization reaction. The stability of nitrile oxides is conditioned by their substitution at the α-position. Alkyl nitrile oxides are very reactive while vinylic, arylic, or sterically hindered α,α-disubstituted nitrile oxides are described to be moderately stable at room temperature and reactive only when heated.[13] We prepared a set of three dialdehyde precur-

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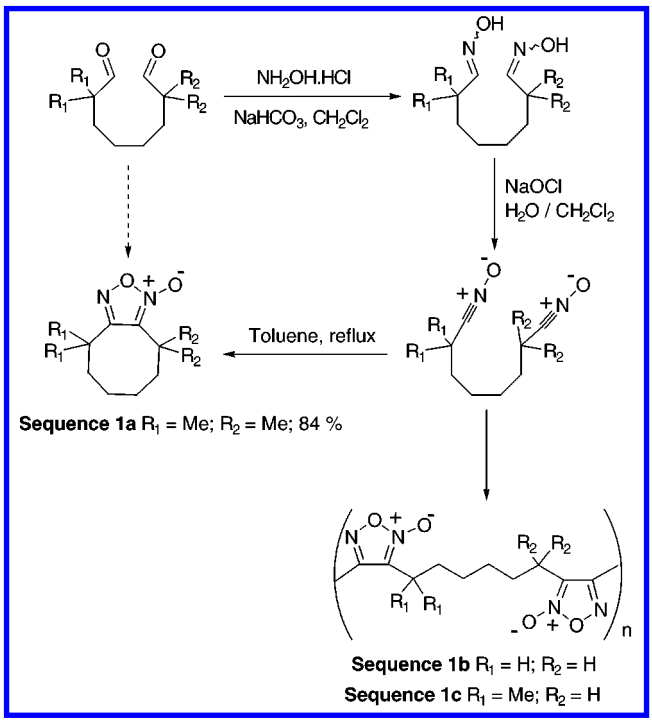
Scheme 1



sors of all possible combinations of stable/reactive nitrile oxides (Scheme 1).

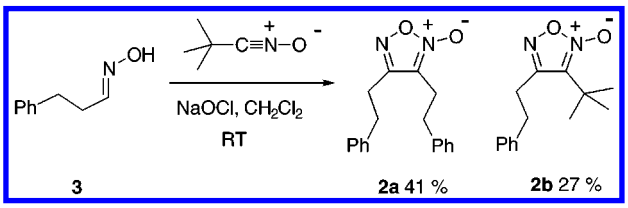
Dialdehyde **1a** was quantitatively transformed into the corresponding dioxime. This upon treatment with sodium hypochlorite led to a stable bis(nitrile oxide) that could be kept for hours under nitrogen at room temperature or for an extended period of time at −20 °C. However, at −20 °C, after several weeks we noticed that bis(nitrile oxide) tended to oligomerize slowly into polyfuroxans. Therefore, for each experiment the bis(nitrile oxide) was freshly prepared.

The cyclization step was performed by the slow addition of a solution of bis(nitrile oxide) (sequence **1a**) to refluxing toluene. After the addition, the mixture was refluxed for a further 2 h, concentrated under vacuum, and purified by silica gel chromatography. Thus, in three steps/one purification process the eight-membered carbocyclic compound was isolated in 84% overall yield.

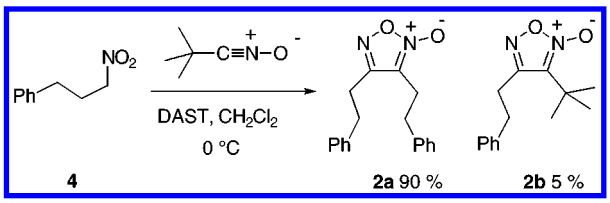
For substrates **1b** and **1c**, one or both aldehydes led to reactive alkyl nitrile oxides preventing all attempts from the isolation of the corresponding bis(nitrile oxide) intermediates. To favor the cyclization over the oligomerization process, we tried to generate the bis(nitrile oxides) under high dilution conditions, and cyclization was carried out at high temperature. Only complex mixtures could be obtained in which traces of cyclic products could be detected by NMR. This observation seems to prove that both substrates **1b** and **1c** react intermolecularly as soon as they are formed. This limitation reflects the basic problem with intramolecular cyclization—to avoid competing intermolecular reactions—which is most difficult to achieve when the intermolecular processes are favored by interaction of more reactive groups.

However, to evaluate further the scope and limitations of cross condensations between stable and reactive nitrile oxides, we generated reactive, unstable nitrile oxides in the presence of a stable one (Scheme 2).

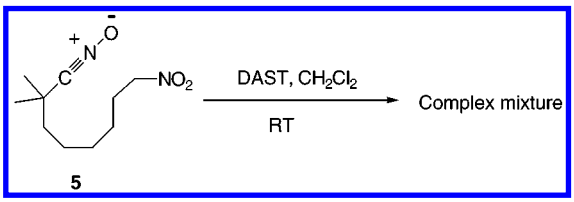
Scheme 2



Scheme 3



Scheme 4



Alkyl oxime **3** was slowly added to a mixture of *tert*-butyl nitrile oxide and sodium hypochlorite at room temperature. Analysis of the reaction mixture showed the presence of only two of the three possible combinations of dimers. Furoxan, formed by dimerization of the reactive nitrile oxide **2a,** was predominant, while the one arising from cross coupling was minor. As expected, furoxan formed by dimerization of *tert*-butyl nitrile oxide was not detectable in the crude. At low temperature, the formation of the nitrile oxides by reaction of oximes and sodium hypochlorite became very slow. Therefore, for further studies of cross coupling at low temperature the reactive nitrile oxide was generated in situ by treatment of the primary nitro derivative **4** with DAST[14] (Scheme 3).

Two conditions were tested, (i) addition of DAST to a mixture of *tert*-butyl nitrile oxide and primary nitroalkyl at −30 °C and (ii) addition of the nitro compound to a mixture of *tert*-butyl nitrile oxide and DAST. In both cases, similar results were obtained. Symmetrical furoxan **2a** was formed predominantly in 90% yield by the dimerization of reactive nitrile oxide. The presence of 5% of furoxan **2b** arising from the cross condensation of the stable and the reactive nitrile oxide could also be detected. These results show clearly that the formation of unsymmetrical furoxans by intermolecular condensation of a reactive and a stable nitrile oxide is problematic because hindered nitrile oxides appear to be poor dipolarophiles. At low temperature they are not reactive, while at high temperature they undergo dimerization.

In a last attempt, we prepared a bifunctional compound **5** bearing both the stable nitrile oxide and the primary nitroalkyl function (Scheme 4).

Addition of this bifunctional compound **5** to a solution of DAST at −30 °C or at 30 °C or addition of DAST to a dilute solution of the bifunctional compound resulted in

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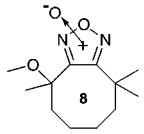
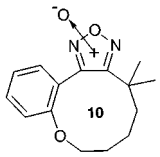
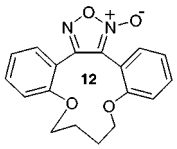
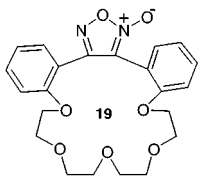
Table 1

Entry	Cyclic Structure	Yield
1		82 %
2		80 %
3		86 %
4		85 %

the formation of complex mixtures in which mass spectral analysis showed a mixture of dimers, trimers, and mainly oligomers.

Alkyl nitrile oxides revealed to be highly reactive intermediates, both as dipoles and as dipolarophiles favoring homo dimerization over cross-condensation with stable nitrile oxides. Thus, our studies demonstrate clearly that the prerequisite to favor cyclization over oligomerization is to utilize dialdehydes that lead to stable bis(nitrile oxides) as substrates. After isolation, they can efficiently be subjected to cyclization. In Table 1 are the summarized results obtained by different combinations of stable nitrile oxides leading to carbo- or to heterocyclic structures of different sizes. In all cases, the cyclic compounds were obtained as the major products. Dimerization of symmetrical (entries 1 and 2) as well as nonsymmetrical dialdehydes (entries 3 and 4) gave the cyclic products in good yields.

During the dimerization process, one of the nitrile oxides acts as a dipole whereas the other acts as a dipolarophile. Thus, in the case of nonsymmetrical dialdehydes (entries 1 and 2), a mixture of the two regioisomeric furoxans was obtained without significant selectivity.

Interestingly, we observed that the ring size has little influence on the yield of the reaction. Medium strained ring structures such as 8-, 10-, and 12-membered rings were consistently obtained in good yields, 82% (entry 1), 80% (entry 2), and 86% (entry 3), respectively. A larger 19-membered ring was also obtained in 85% yield (entry 4). It is worth noting that in contrary to many other reactions, the steric hindrance in this reaction is not a drawback.

In summary, we describe a useful procedure for the preparation of carbocyclic structures. Thermal dimerization of stable bis(nitrile oxides) allow the ring closure of a large range of sizes in fairly good yields. In addition, the mild reaction conditions required for the reaction are compatible with a large variety of functional groups. However, the method revealed to be restricted to stable bis(nitrile oxides). Considering the wide panel of substituents that are able to stabilize or to temporarily stabilize the nitrile oxides, e.g., dithioacetals, the reaction appears nevertheless very useful. In addition, the furoxan moiety introduced during the cyclization process allows an easy access to interesting 1,2-functionalities present in many macrocyclic structures. Therefore, this new C−C bond-forming ring-closing reaction is of synthetic interest and is complementary to other existing methodologies.

Experimental Part

General Methods. Thin-layer chromatograms (TLC) were performed on precoated silica gel 60 F254 plates (Merck, 0.25 mm.). Flash chromatography separations were performed on silica gel (Merck 60, 230−400 mesh). Reaction vessels were flame-dried and were allowed to cool under an inert atmosphere. Solvents were freshly distilled over appropriate desiccants prior to use.

Transformation of Dialdehyde into Bis(nitrile oxide). To a solution of dialdehyde (sequence 1a**)** (1.10 g, 5.55 mmol) in 30 mL of methylene chloride at 0 °C were added successively hydroxylamine hydrochloride (1.91 g, 27.7 mmol), sodium carbonate (1.52 g, 14.42 mmol), and 10 mL of water. After the mixture was stirred for 24 h at room temperature, the organic layer was separated and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to afford the dioxime (1.20 g, 5.26 mmol) in 95% yield.

The crude dioxime (200 mg, 0.88 mmol) was then dissolved in 8 mL of methylene chloride followed by the dropwise addition of a solution of sodium hypochorite (2.5 M, 8 mL, 5 equiv) at 0 °C. After 2 h of vigorous stirring at 0 °C, the organic layer was separated and the aqueous layer was extracted with methylene chloride (3 × 20 mL). The combined organic phase was washed with brine (40 mL), dried over sodium sulfate, and concentrated at 0 °C under reduced pressure to afford the bis(nitrile oxide) (196 mg, 0.88 mmol)) in quantitative yield.

Intramolecular Cyclization. The cyclization step was carried out by adding a solution of bis(nitrile oxide) (196 mg, 0.88 mmol) in anhydrous toluene (20 mL) to refluxing anhydrous toluene (40 mL) over a period of 4.5 h. After an additional 2 h under reflux, the reaction mixture was concentrated under reduced pressure and the product was purified by column chromatography on silica gel using ether/hexane 9/1. The cyclic product (sequence 1a) was obtained in 84% yield (164 mg, 0.64 mmol) as white crystals.

4,4,9,9-Tetramethylperhydrocycloocta[*c*]furazan 1-oxide: R_f = 0.40 (hexane/ether; 9/1); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (6H, s), 1.51 (6H, s), 1,30−2.05 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 23.6, 24.7, 32.1, 34.2, 37.0, 37.8, 39.6, 122.5, 163.0; IR 1562 (C=N−O) 1455 (C=N$^+$(O$^-$)−O, 1376 (N−O) cm^{-1}; MS (CI/NH_3) *m*/*z* 242 (M + NH_4) $^+$. Anal. Calcd for $C_{12}H_{20}N_2O_2$ (224.1): C, 64.30; H, 8.91; Found: C, 64.72; H, 9.19.

9-Methoxy-4,4,9-trimethylperhydrocycloocta[c]furazan 1-oxide: R_f = 0.68 (hexane/ethyl acetate 7/3); colorless oil, isolated as a 2/1 mixture of two regioisomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26, 1.32, 1.44, 1.49, 1.68, 1.77 (9H, 6xs), 1.20−2.10 (8H, m), 3.13, 3.18 (3H, 2 × s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 22.9, 23.5, 23.7, 23.8, 24.3, 24.6, 25.4, 27.6, 32.8, 34.0, 36.4, 36.6, 37.0, 41.3, 41.5, 51.0, 51.7, 76.7, 77.3, 115.9, 122.6, 158.7, 165.9; IR 1573 (C=N−O), 1458 (C=N$^+$(O$^-$)−O, 1364 (N−O) cm^{-1}; MS (CI/NH_3) *m*/*z* 258 (M + NH_4) $^+$. Anal. Calcd for $C_{12}H_{20}N_2O_3$(240.1): C, 60.02; H, 8.32. Found: C, 59.95; H, 8.22.

4,4-Dimethyl-4,5,6,7-tetrahydro-8*H*-9-oxabenzo[*b*]furazancyclodecene 1-oxide: R_f = 0.64 (hexane/ethyl acetate 8/2); white solid, isolated as a 1/1 mixture of two regioisomers; mp = 184 °C-186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.40 (8H, m), 1.50−1.65 (2H, m), 1.70−1.85 (2H, m), 4.29 (2H, t, J = 6 Hz), 7.09−2.27 (2H, m), 7.29−7.32 (1H, m), 7.48−7.54 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.4, 26.1, 26.3, 36.9, 37.2, 39.5, 69.6, 69.8, 116.0, 116.8, 120.4, 121.9, 122.6, 131.3, 132.1, 155.5,

158.7; IR 1577 (C═N−O), 1458 (C═$N^+(O^-)$−O, 1385 (N−O) cm^{-1}; MS (CI/NH_3) *m*/*z* 292 (M + NH_4) $^+$. Anal. Calcd for $C_{15}H_{18}N_2O_3$(274.2): C, 65.71; H, 6.56. Found: C, 65.82; H, 6.50.

9,10,11,12-Tetrahydro-8,13-dioxadibenzo[*g*,*k*]furazano-[3,4-*i*]cyclododecene 1-oxide: R_f = 0.50 (hexane/ethyl acetate 8/2); white solid; mp = 192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (4H, m), 3.91 (2H, m), 4.23 (2H, m), 6.80−7.05 (5H, m) 7.30−7.44 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 26.6, 68.9, 69.9, 109.0, 109.2, 113.3, 113.5, 120.7, 120.8, 130.5, 130.9, 156.4, 156.9; IR 1601 (C═N−O), 1462 (C═$N^+(O^-)$−O cm^{-1}; MS (CI/NH_3) *m*/*z* 342 (M + NH_4) $^+$. Anal. Calcd for $C_{18}H_{16}N_2O_4$(324.2): C, 66.68; H, 4.93. Found: C, 66.56; H, 5.15.

9,10,12,13,15,16,18,19-Octahydro-8,11,14,17,20-pentaoxadibenzo[*n*,*r*]furazano[4,3-*p*]cyclononadecene 1-oxide: R_f = 0.64 (hexane/ethyl acetate 8/2); white solid; mp = 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (2H, t, J = 5 Hz), 3.6−3.7 (8H, m), 3.7−3.8 (4H, m), 4.17 (2H, t, J = 5 Hz), 6.85−6.92 (2H, m), 6.95−7.10 (3H, m), 7.35−7.50 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.4, 68.8, 69.1, 69.9, 70.6, 70.9, 71.0, 71.3, 112.7, 113.5, 114.0, 120.8, 121.1, 129.7, 130.6, 131.8, 132.4, 156.4, 157.1; IR 1601 (C═N−O), 1462 (C═$N^+(O^-)$−O cm^{-1}; MS (CI/NH_3) *m*/*z* 446 (M + NH_4) $^+$. Anal. Calcd for $C_{22}H_{24}N_2O_7$ (428.2): C, 61.70; H, 5.60. Found: C, 61.82; H, 5.71.

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