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Functionalization of the benzobicyclo[3.2.1]octadiene skeleton via photocatalytic and thermal oxygenation of a furan derivative

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ABSTRACT

A simple and efficient protocol is utilized for the synthesis of novel functionalized benzobicyclo[3.2.1]octadiene derivatives by photocatalytic oxygenation of a furan derivative using an anionic free-base porphyrin as well as cationic and anionic manganese(III) porphyrins under different reaction conditions. The course and yields of these reactions were compared to those of the thermal reaction using *m*-chloroperbenzoic acid as the oxidizing agent. The deviating reaction pathways with anionic and cationic metalloporphyrins may be attributed to simultaneous electronic and steric effects. Application of free-base and metalated water-soluble porphyrins for photocatalytic oxygenation of the furan ring fused to the rigid methano-bridged skeleton proved to be regioselective and flexible compared to the thermal reactions with mCPBA, giving at the same time novel potentially biologically active bicyclo[3.2.1]octenes with the basic skeleton of which is incorporated in many natural compounds.

Earlier studies indicated that photochemical reactions for the synthesis of rigid methano-bridged heteroaromatics **1**–**3** (Fig. 1) also offered suitable pathways toward oxygenated derivatives **4**–**6**[1] which cannot be produced (at least with sufficient selectivity) via thermal processes.

In continuation of our interest in the preparation of new benzobicyclo[3.2.1]octadiene derivatives, we turned our attention to the utilization of photocatalytic oxygenation of bicycloalkenes containing a fused furan ring. In this case the starting substrate was compound **1** (Fig. 1). Functionalization of this type of furo polycycle affords new polycyclic epoxides, enediones, ketones, alcohols, and/or hydroperoxides. Their structures represent basic frameworks of many biologically active and important substances isolated from Nature.[2,3] On the other hand, the fused heteroaromatic benzobicyclo[3.2.1]octadiene **1** can be easily obtained from the corresponding *o*-vinyl substituted hetero-stilbene and proved to be a convenient substrate for efficient one-step photochemical ring closure.[4,5]

Both metalated and free-base porphyrins were found to be efficient in photocatalytic oxygenation of cycloalkenes[6–8] and other unsaturated heteroaromatics.[9] While free-base porphyrins can be utilized as sensitizers for the generation of singlet oxygen,[9–13] metalloporphyrins are much more versatile as photocatalysts. Their application can result in autooxidation reactions, hydroxylations, or direct oxygen transfer yielding epoxides.[14,15] Cationic manganese(III) porphyrins proved to be effective for catalytic oxygenation of α-pinene. In aqueous systems, at relatively low substrate:catalyst ratio (S/C = 500) its selective epoxidation was observed, strongly deviating from the case of aprotic organic solvents such as benzene or toluene, where allylic hydroxylation products were formed.[6] Photocatalytic epoxidation of cyclooctene was achieved in acetonitrile with various metalloporphyrins.[8]

These precedents inspired us to study the photocatalytic activity of water-soluble manganese(III) porphyrins for the oxygenation of benzobicyclo[3.2.1]octadiene derivative **1**, having a basic skeleton similar to that of previously studied naturally occurring cycloalkenes. Our aim was to compare the oxygenation pathways of this furo bicyclic structure **1** in both a thermal reaction involving mCPBA and a photocatalytic processes mediated by free-base and manganese(III) porphyrins. Anionic and cationic metalloporphyrins were used in our experiments (Fig. S1). Differences and similarities in these pathways may shed light on the mechanisms of the various oxygenation processes, giving hints for appropriate choice of the catalyst and other conditions to achieve efficient conversion with high selectivity. The charge on the ligand, influencing its Lewis basicity may affect the catalytic activity of the complex through the metal center.

In the thermal reaction of **1** using mCPBA (Scheme 1) the enedione **8** is thought to be produced via rearrangement of intermediate epoxide **7** formed initially from **1**.[16] Since there are two epoxidation sites on furan **1**, we concur with the literature suggestion that the initial epoxidation occurs at the substituted cyclohexyl side of the furan ring as indicated in the left sequence in Scheme 1. This is reasonable on the basis of the concept that epoxidation should

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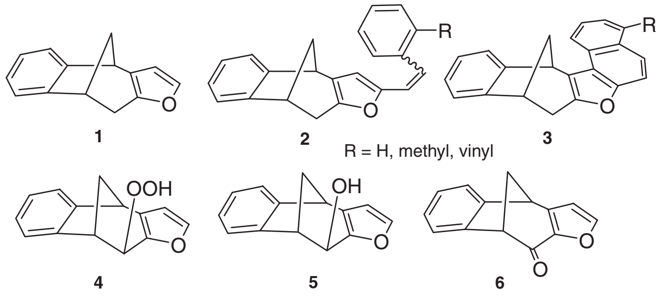


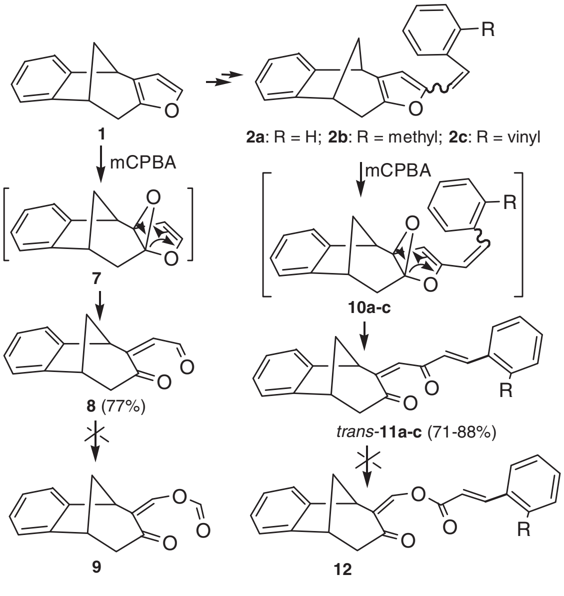
Figure 1. Structures of known rigid methano-bridged heteroaromatics **1**–**6**.

occur at the double bond bearing the more electron-donating group.[17] Therefore, we propose the formation of **8** from the rearrangement reaction of epoxide **7**. Further oxygenation to **9** did not take place. As described in our previous paper,[18] substituted styryl derivatives **2a–c** (Scheme 1) are easily available from benzo-furo bicyclic structure **1**. These compounds were also submitted to additional thermal transformations using mCPBA, giving all *trans*-**11a**–**c** (formed via intermediates **10a**–**c**) in good yields (71–88%). Further oxygenation to compounds **12** was not observed.

Scheme 2 shows the products **13**–**17** of light-induced oxygenation of **1**, using different porphyrins as photocatalysts. Blank experiments were also carried out. No permanent change was observed in the dark (after stirring air-saturated solutions containing both substrate and catalyst for 2 h), nor upon irradiation in the absence of porphyrin. These observations clearly indicated that the substrate does not undergo any thermal reaction even in the presence of ground-state porphyrins.

Since under the experimental conditions applied[19] [irradiation with polychromatic light (λ >380 nm)] the porphyrin photocatalysts absorb exclusively in these systems, the chemical changes observed can be attributed unambiguously to photoinduced reactions involving the excited states of these macrocyclic compounds.

The longer-lived triplet state plays a role in the photoinduced reactions if a free-base porphyrin (H_2TSPP^{4-} in our case) is the photoactive species in the system. Thus, it functions as a sensitizer generating singlet oxygen via triplet quenching by the dissolved ground-state oxygen molecules.[20] The product in this case is hydroxybutenolide derivative **15** (Scheme 2), which cannot be detected in any other oxygenation process studied in this work, neither in the thermal oxidation with mCPBA, nor with manganese(III) porphyrin photocatalysts. This observation clearly indicates that this is the only case when singlet oxygen is the oxidative agent, the reaction pathway leading to a final product deviating from all the others. According to the previous studies on oxygenation of cycloalkenes, the mechanism of the reaction is quite complicated, involving at least 3–4 elementary steps.[9,10,13]

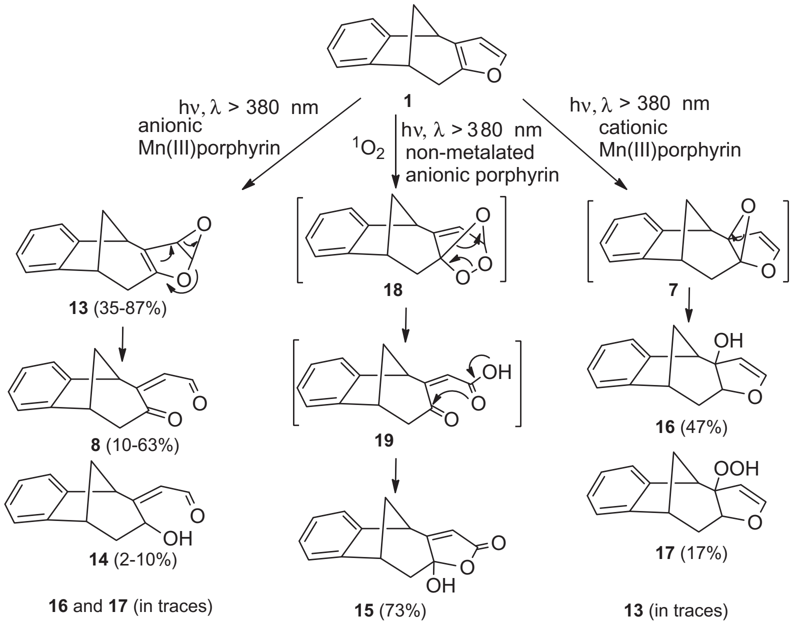


Scheme 1. Proposed reaction pathways for the thermal reactions of **1** and **2**.

In the presence of anionic Mn(III)TSPP^{3-}, under similar conditions as in the case of the corresponding free base (air-saturated solution, pH 7), epoxide **13** and furan ring-opened **8** and **14** products were detected in appreciable amounts (Scheme 2, Table 1). This observation differs significantly from that published by Hennig et al.[15] in which this anionic manganese(III) porphyrin did not display any photocatalytic activity regarding the oxygenation of α-pinene in a similar system. We had the same experience during the preliminary investigation of *endo*-6-phenyl-6,9-dihydro-5*H*-5,9-methano-benzocycloheptene,[21] a compound similar to **1**, but without a furan ring, using Fe(III)TSPP^{3-} photocatalyst. However, in the presence of this catalyst, **1** was also photooxygenated to the same products as those observed with the manganese(III) porphyrin. These results clearly indicate that the double bond in the furan ring is more reactive than that in a saturated hydrocarbon environment. This phenomenon may be attributed to the mesomeric effect of the free electron pairs on the oxygen atom. Nevertheless, in the presence of cationic manganese(III) porphyrins an epoxy-derivative was also obtained as the main product of the oxygenation of α-pinene.[15] This observation suggests that the positively charged porphyrin ligand is significantly better able to promote oxygenation on the double bond of a cycloalkene than the negatively charged example.

Modification of the experimental conditions (pH or oxygen concentration) resulted in changes in the ratio of the products but did not cause formation of further new species (Table 1). Thus, increasing the pH (to 10) enhanced the quantity of the epoxidized product **13** from 35% to 87%. This phenomenon suggests that the higher pH apparently hinders further oxidation of this derivative, strongly diminishing the amounts of ring-opened products. This effect may be attributed to the role of protons in the disproportionation reaction giving an Mn(V) species (see later, Eq. 3). Hence, formation of this highly reactive intermediate is reduced at higher pH, decreasing the chance of further oxidation of **13**, and thus promoting its accumulation. Bubbling oxygen instead of air significantly increased the amounts of the products **13** and **14** from 35% to 70% and from 2% to 10%, respectively (Table 1). As Scheme 2 indicates, application of cationic manganese(III) porphyrin [Mn(III)TMPyP^{5+}] did not lead to the formation of different products, but the hydroxy **16** and hydroperoxy **17** derivatives became the main products (formed via intermediates **18** and **19**), while the epoxidized compound **13** was formed only in traces. This phenomenon indicates that a change in the sign of the ligand charge strongly modifies the distribution of the oxygenation products. The main products with the anionic photocatalyst become trace products with the cationic metalloporphyrin and vice versa, that is, competition of the simultaneous oxygenation reactions is governed by the ligand charge. Besides, as mentioned before, the cationic complex proved to be effective in oxygenation of various cycloalkenes, while the anionic example was less efficient or inactive.[6,15] Apparently, the lower Lewis basicity of the porphyrin ligand promotes oxygenation on C=C bonds. This was confirmed by flash photolysis experiments with manganese(III) porphyrins possessing substituents of various electron demand.[22,23]

As earlier studies[6] and more recent publications[8,23] have indicated, in the case of manganese(III) porphyrins as photocatalysts, (P)Mn^{IV}=O and (P)Mn^{V}=O intermediates play the key role of the in situ generated reactive species in the oxygenation of cycloalkenes. The formation of (P)Mn^{V}=O in primary photochemical reac-



Scheme 2. Proposed reaction pathways for the photocatalytic oxygenation reactions of **1** (pH 7, air-saturation unless otherwise stated; see Table 1 for anionic Mn(III)porphyrin).

Table 1
Photoproducts with yields (%) obtained using anionic manganese(III) porphyrin under various relevant experimental conditions.[a]

Compound	8	13	14	16	17
% (pH 7, air-saturation)	63	35	2	Traces	Traces
% (pH 10, air-saturation)	10	87	3	Traces	Traces
% (pH 7, oxygen-saturation)	20	70	10	Traces	Traces

[a] In the cases of the free base and cationic manganese(III) porphyrin Scheme 2 unambiguously displays the products and yields, hence they are not provided in this Table.

tions was observed in acetonitrile, as a consequence of heterolytic cleavage of the O–Cl bond in the axially coordinated perchlorate counterion.[22,23] (P)Mn^{IV}=O was produced by photoinduced homolysis of the O–Cl or O–N bond of axially coordinated chlorate or nitrate, respectively, in acetonitrile,[22,23] or via a ligand-to-metal charge-transfer process (also a photoinduced homolysis but that of the metal-ligand bond) with chloride or hydroxide axial ligands in aqueous systems.[6,15] In the latter case the Mn(II) species was formed in the primary photochemical step (Eq. 1) followed by the coordination of oxygen (Eq. 2).

$$(\mathrm{P})\mathrm{Mn^{III}OH} + h\nu \rightarrow (\mathrm{P})\mathrm{Mn^{II}} + {}^{\cdot}\mathrm{OH} \tag{1}$$

$$2(\mathrm{P})\mathrm{Mn^{II}} + \mathrm{O_2} \rightarrow 2(\mathrm{P})\mathrm{Mn^{IV}{=}O} \tag{2}$$

Eq. 2 is an overall reaction comprising several steps.[15] Since our experiments were carried out in water–acetone solvent mixture, hydroxide or water was axially coordinated to the Mn(III) center. Accordingly, hydroxyl radicals formed in the primary photochemical step most probably react with the organic solvent. The Mn(IV) complexes readily disproportionate, giving highly reactive manganese(V)-oxo species (Eq. 3).[22,23]

$$2(\mathrm{P})\mathrm{Mn^{IV}{=}O} + \mathrm{H^+} \rightleftharpoons (\mathrm{P})\mathrm{Mn^{V}{=}O} + (\mathrm{P})\mathrm{Mn^{III}OH} \tag{3}$$

Disproportionation is much faster than synproportionation in this equilibrium system, moreover, a polar solvent promotes the previous process, thus it occurs with nearly a diffusion-controlled rate constant.[22] The rate constants for epoxidation of olefins are several orders of magnitude higher for manganese(V)-oxo porphyrins than for the corresponding Mn(IV) species. Hence, (P)Mn^{V}=O can be considered as the major oxidant in the photocatalytic oxygenations in our systems.

As Scheme 2 indicates, the positively charged porphyrin ligand promotes electrophilic attack on the inner double bond of the furan ring, while the anionic catalyst favors the outer C=C bond. This phenomenon may be attributed to simultaneous electronic and steric effects. Compared to the outer double bond, the accessibility of the inner double bond to the oxygen atom coordinated to the bulky macrocyclic complex is sterically hindered, due to its bicyclic environment. From an electronic point of view, this bond is more favored for electrophilic attack as a consequence of the electron-donating effect of the adjacent hydrocarbon (bicycloalkyl) parts of the molecule. Since the lower Lewis basicity of the cationic complex makes the corresponding manganese(V)-oxo intermediate much more electrophilic than the anionic one, in the case of the previous metalloporphyrin the electronic effect governs the reaction pathway, leading to hydroxylation or hydroperoxylation on the inner carbon atoms via an epoxy intermediate. For the less electrophilic anionic complex steric hindrance is the predominant effect, promoting attack at the more accessible outer bond.

All the photoproducts, **8** and **13–17** (Scheme 2), were isolated by repeated thin-layer chromatography and characterized by spectroscopic methods.[19] From the NMR spectra, using different techniques (COSY, NOESY, HSQC, and HMBC) and taking as reference our previous results,[21,24] the structures of all the compounds were determined. All the photoproducts have recognizable patterns in their ^{1}H NMR spectra (Fig. 2) but different numbers of signals in their aliphatic regions, depending on the structure (See Supplementary data). These suggested results were confirmed from their ^{13}C NMR spectra which clearly revealed the structures with characteristic formyl, keto, hydroxy, and/or hydroperoxy groups. Molecular ions *m*/*z* 212 (**8**, **13**, **14**), *m*/*z* 228 (**15**), *m*/*z* 214 (**16**), and *m*/*z* 230 (**17**) indicated that one or two oxygen atoms were incorporated in the starting substrate **1**. The IR spectra of **8** and **13–17** showed characteristic signals for the formyl, keto, hydroxy and/or hydroperoxy groups. The thermal products **11a–c** were isolated by repeated column chromatography and characterized by spectroscopic methods[19] (Fig. S2).

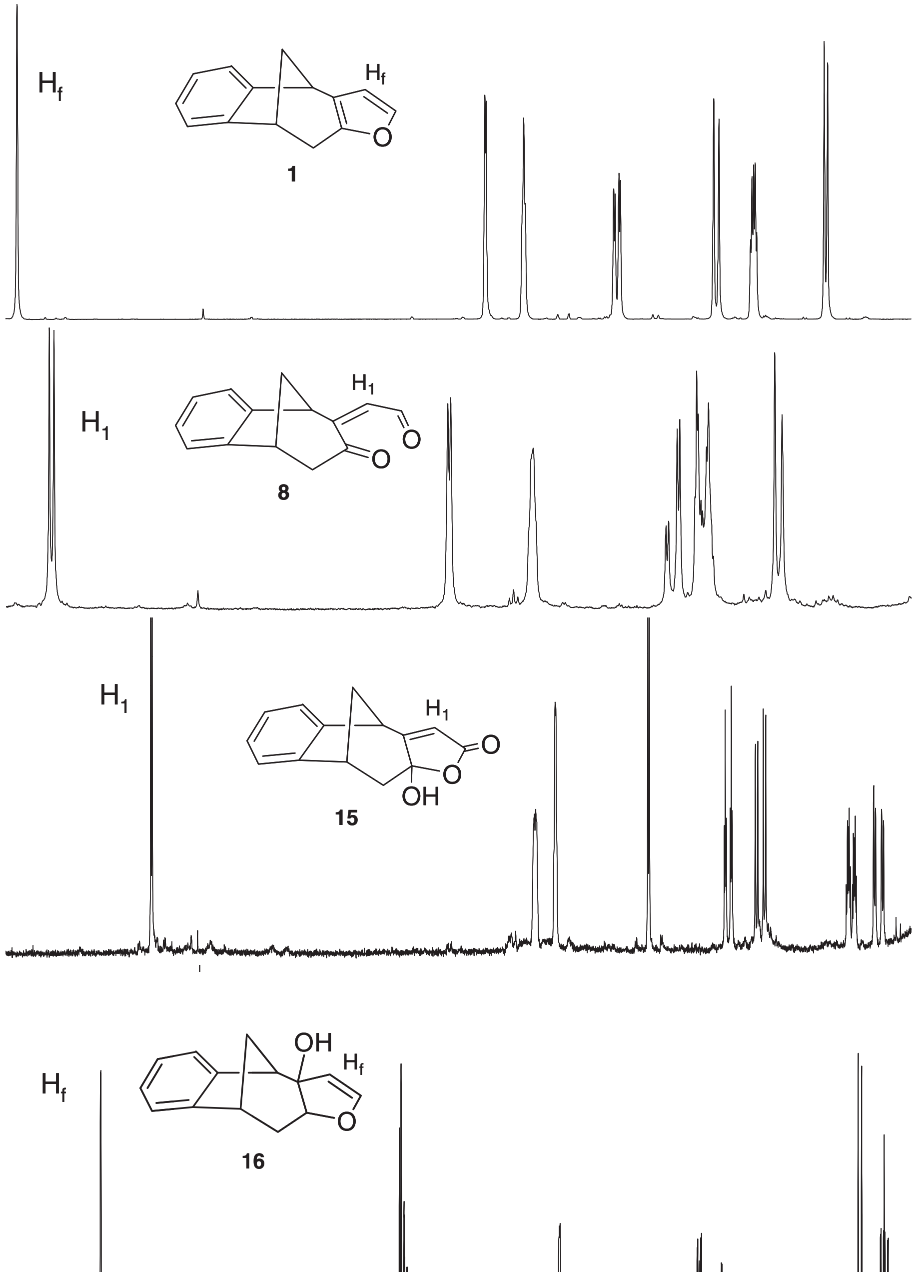


Figure 2. ^{1}H NMR spectra of benzobicyclo[3.2.1]octadienes **1**, **8**, **15**, and **16** (CDCl$_3$, 600 MHz).

In conclusion, a simple and efficient protocol is utilized for the synthesis of functionalized benzobicyclo[3.2.1]octadienes from furan derivative **1** having no characteristic functional groups but reactive double bonds.

Application of free-base and metalated water-soluble porphyrins for photocatalytic oxygenation of furan derivative **1** proved to be flexible compared to the thermal reactions with mCPBA. Excitation of the free-base porphyrin (H$_2$TSPP^{4-}) produces singlet oxygen, the reaction of which with the substrate leads to a hydroxybutenolide derivative. Use of the corresponding manganese(III) porphyrin [Mn(III)TSPP^{3-}] as a photocatalyst results in the formation of epoxidized and furan ring-opened derivatives as the main products, indicating that the preferred target of oxygenation in this case is the outer double bond of the furan ring. In contrast, photocatalysis with cationic manganese(III) porphyrin leads to oxygenation on the inner double bond of the furan ring, forming hydroperoxy- and hydroxy-derivatives. These results demonstrate that the charge on the porphyrin ligand determines the pathway of the oxygenation reaction in this system, offering the possibility of controlling the types and distributions of the final products. Application of water-soluble free-base and metalloporphyrins for oxygenation of organic substrates in water–acetone solvent mixture promotes the easy separation of the products from the catalyst, ensuring the efficient reuse of the latter. This feature is a considerable advantage over the fully hydrophobic systems.

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.076.

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19. *Typical experimental procedure for the photocatalytic oxygenation of **1***. A solvent mixture prepared by addition of the same volumes of acetone and water was used in the photocatalytic experiments. A solution of 40 ml of **1** and the Mn(III) porphyrin (see Fig. S1) was irradiated with a 70 W tungsten halogen immersion lamp (Philips, λ_{ir} >380 nm) in a thermostated 50 ml cylindrical photoreactor. A stream of air or oxygen was passed through the solution at rt over 2 h, also ensuring vigorous stirring. The concentration conditions were: S/C = 100, Mn(III)porphyrin = 0.00144 mol and **1** = 0.144 mol. After termination of the photolysis, acetone was removed by vacuum distillation. The remaining two phases were separated by standard methods. The water-insoluble oxygenation products remained in the organic phase and there was no unreacted substrate. The photoproducts **8** (10–64% yield) and **13**–**17** (**13**: 35–87%, **14**:2–10%, **15**: 73%, **16**: 47%, **17**: 17%) (Scheme 2), were isolated by repeated thin-layer chromatography and characterized by spectroscopic methods.
    *Typical experimental procedure for the thermal oxygenation of **1** and **2***. To compound **1** or **2** in CH_2Cl_2 (c = 0.14 M) at −10 °C,1 equiv of mCPBA in CH_2Cl_2 was added and the mixture stirred for 2.5 h at rt. After removal of the solvent, H_2O was added to the residue, which was next neutralized with saturated $NaHCO_3$ solution and the products were extracted with diethyl ether. The thermal products **8** and **11a–c** (Scheme 1) were isolated by repeated column chromatography on silica gel using petroleum ether/CH_2Cl_2 mixture as eluent and characterized by spectroscopic methods giving the following yields: **8**: 77%, **11a**: 88%, **11b**: 83% and **11c**:71%.
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