Pergamon

Tetrahedron Letters 41 (2000) 8553–8557

TETRAHEDRON
LETTERS

Synthesis of medium and large ring heterocycles by photoinduced intermolecular and intramolecular electron transfer reactions of tetrachlorophthalimides with alkenes

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Received 23 May 2000; revised 24 August 2000; accepted 7 September 2000

Abstract

Photoinduced intermolecular and intramolecular electron transfer reactions of *N*-(ω-hydroxyalkyl)-tetrachlorophthalimide with alkenes led to the formation of medium to large sized heterocyclic rings.

Keywords: photochemistry; tetrachlorophthalimide; electron transfer reactions; polycyclic heterocyclic ring.

The construction of medium and large heterocyclic ring systems has constantly been an important task in organic synthesis.[1] Recently, photoinduced intramolecular cyclizations of *N*-substituted phthalimides have been successfully used for the syntheses of medium to large ring systems.[1,2] Most of these syntheses are based on intramolecular single electron transfer (SET) reactions between the photoexcited phthalimide moiety and a remote electron donor group (a benzylic position,[3] alkoxy,[4] thioalkyl,[5] dialkylamino,[6] or trimethylsilyl[7] group) at the *N*-substituted phthalimide side chain. Subsequent proton transfer or trimethylsilyl cation transfer from the donor cation radical to the carbonyl ketyl radical anion followed by radical pair collapse resulted in ring closure to give ring systems with donor group incorporation. In a few examples, photoinduced intramolecular SET between the phthalimide and an alkene followed by solvent trapping of the cationic center of the alkene and radical pair recombination furnish ring products with solvent incorporation.[8] Recently, another approach in which side chain decarboxylation induced by SET between the excited phthalimide and a remote carboxylic acid anion at the side chain and subsequent radical pair recombination has been used for the construction of medium to large rings without donor or solvent incorporation.[9] Photoinduced intermolecular electron transfer reactions with phthalimides as electron acceptors, however, have

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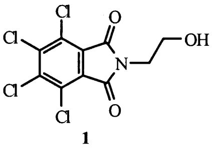
PII: S0040-4039(00)01520-3

never been applied to the construction of medium to large ring systems. We report here new ring forming reactions based on both inter- and intramolecular SET reactions between photoexcited *N*-substituted 4,5,6,7-tetrachlorophthalimide (TCP) and alkenes, taking advantage of the exceedingly strong electron acceptor ability of TCP.[10]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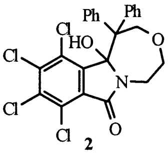
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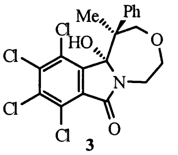
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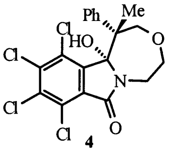
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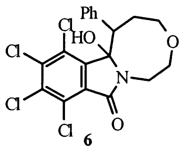
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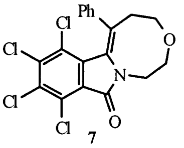
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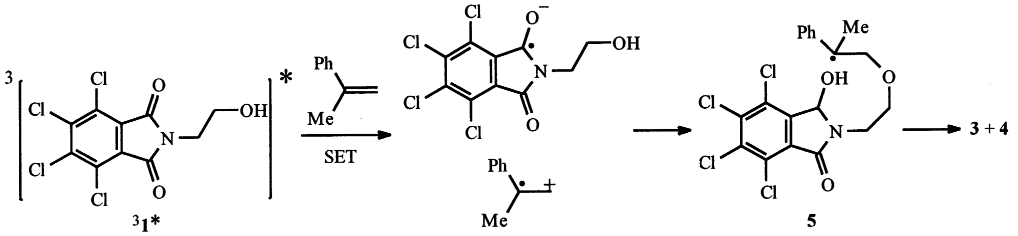
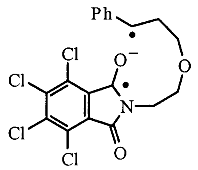
Irradiation of *N*-(2-hydroxyethyl)-4,5,6,7-tetrachlorophthalimide **1** in the presence of 1,1-diphenylethene in benzene afforded the three ring product **2** in 77% yield. Similar irradiation of **1** with α-methylstyrene in benzene gave the three-ring products **3** and **4** as a pair of diastereoisomeric racemates in 78% yield. Two chiral centers are created during the ring formation, and the diastereoselectivity is quite good with a product ratio **3** (the *SS–RR* racemate)/**4** (the *RS–SR* racemate) of 2.5:1. Mechanistically, these reactions are initiated by SET from the alkene to the triplet excited **1**.[12] Capture of the cationic center by the hydroxy group at the side chain of **1** followed by radical pair recombination gave the products (Scheme 1). The regioselectivity seen in these products manifested the charge and spin density distributions in the cation radicals of the alkenes. Therefore, spin densities and positive charge are largely concentrated at the terminal carbon atom in the cation radicals of these α-substituted styrenes, and nucleophilic capture of the cationic center leads to the formation of benzylic radicals (e.g. in **5**), as has been suggested by experimental results[14] and AM1 MO calculations.[15]



Scheme 1.

Photolysis of a benzene solution of **1** and phenylcyclopropane afforded the eight-membered ring product **6** in 82% yield, which on treating with BF_3–etherate gave the dehydration product **7** quantitatively. In this case, SET from phenylcyclopropane to ^{3}**1***[16] leads to the formation of cyclopropane cation radicals which undergo ring opening in the presence of an alcohol as a nucleophile to give the benzylic radical **A**,[16] subsequent radical pair recombination furnishes product **6**.



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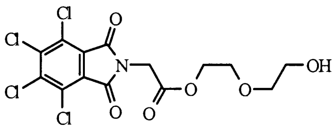

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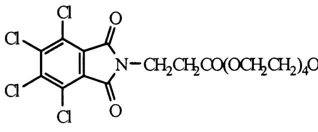

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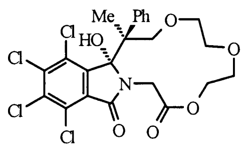

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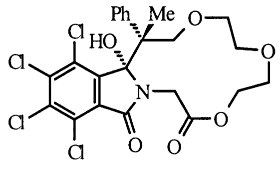

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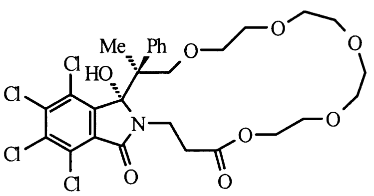

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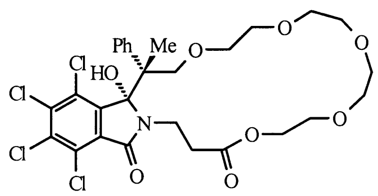

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These ring forming reactions are efficient in view of the high yields of the products and the convenient reaction conditions.[17] High dilution of reactants which is often a prerequisite in unimolecular reactions is not needed here, indeed rather high concentration of the reactants (0.025 M in TCP) can be used. Furthermore, by changing the alkenes and the side chain in the phthalimide, this type of intermolecular SET reaction between *N*-substituted TCP and alkenes can become very versatile in constructing ring systems of different sizes and structures. As examples to illustrate this versatility, it was found that photolysis of the *N*-phthaloylglycine derived **8** with α-methylstyrene in benzene gave the 13-membered lactones **10** and **11** as a pair of diastereomers in 50% yield. The diastereoselectivity here in the ring formation slightly favors isomer **10** with a product ratio of 3:2. Similar photolysis of the *N*-phthaloyl-β-alanine derived **9** with α-methylstyrene in benzene gave the 20-membered ring products **12** and **13** (Fig. 1) as a pair of diastereomers in 16 and 14% yield, respectively. Therefore, the diastereoselectivity is seen to decrease with an increase in the ring size as the steric strain for the ring formation is lessened for the more flexible larger rings.

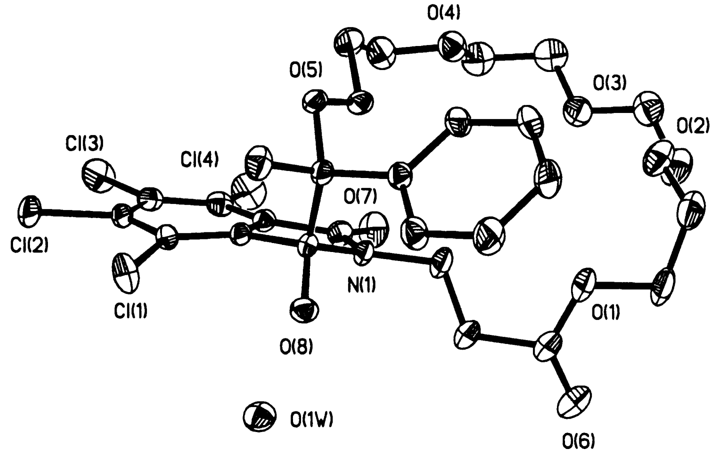
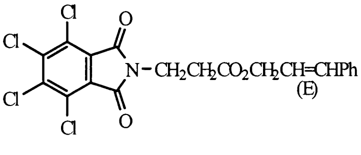


Figure 1. ORTEP drawing of **13**

We have found in our previous work[18] that photoinduced reactions of *N*-methyl TCP with alkenes in benzene or in MeCN afforded spiroxetane products exclusively, in sharp contrast with the situation with *N*-methylphthalimide where photoinduced reactions with alkenes normally afforded benzazepinedione products.[2] We have therefore tried an intramolecular version of this reaction by preparing compound **14** (*E*-isomer) and photolyzing it in benzene and found that this gave the diastereoisomeric five-ring products **15** (62% yield) (Fig. 2) and **16** (5% yield) with an oxazonine ring annelated by a spirooxetane ring. A small amount (17% yield) of the *Z*-isomer of the starting **14** was also obtained after the photolysis.



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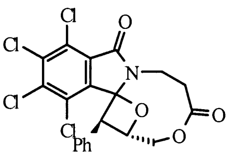

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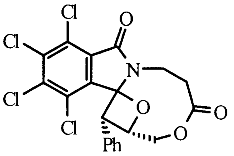

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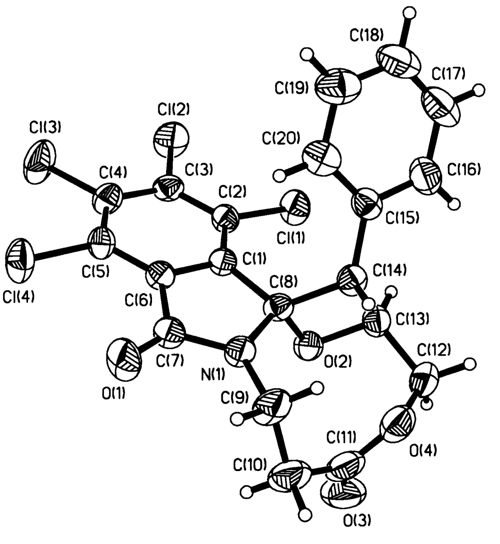

Figure 2. ORTEP drawing of **15**

In summary, photoinduced inter- and intramolecular SET reactions of *N*-(ω-hydroxyalkyl)tetrachlorophthalimide with alkenes lead to the formation of polycyclic heterocyclic ring systems. While this proved most efficient in the construction of medium sized rings (e.g. the eight membered oxazocines and the nine membered oxazonines), which are the most difficult to synthesize by conventional cyclization reactions,[1] they could also be used for the convenient syntheses of large ring systems. These novel ring formation reactions also illustrate the synthetic potential of the use of electron acceptors with a side chain that bears a nucleophilic group (such as a hydroxyl) in the reaction sequence (photoinduced electron transfer, intermolecular nucleophilic trapping, intramolecular radical pair recombination) for the construction of polycyclic ring systems.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (29772016) and the Natural Science Foundation of Jiangsu Province (BK97017).

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10. TCP has a half wave reduction potential of –0.95 V (SCE, MeCN) and a triplet energy (E_T) of 67 kcal/mol. The reduction potential of the triplet excited state is 1.96 V (SCE) as compared with 1.66 V (SCE) of triplet unsubstituted phthalimide. The absorption maximum of TCP in the UV spectrum is red-shifted to 333 nm from the 293 nm for the unsubstituted *N*-methylphthalimide. Our experimental results showed that irradiation of *N*-(ω-hydroxyalkyl)phthalimide (P) with the alkenes (α-methylstyrene, 1,1-diphenylethene) under conditions as mentioned above resulted in very low conversions of the starting materials and did not lead to significant ring formations even after prolonged photolysis. Another merit in using TCP is the much milder conditions in removing the phthalimide protecting group by hydrolysis for TCP than for P.[11]
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16. Phenylcyclopropane has an $E^{ox}_{1/2}$ of 1.83 V (SCE), the ΔG_{ET} with $^3\mathbf{1}^*$ as estimated by the Weller equation is 5.9 kcal/mol. Phenylcyclopropane cation radicals are apt to undergo an S_N2 nucleophilic attack by alcohols to give ring-opened benzylic radicals. Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, H.; Todd, W. P.; Heinrich, T. *J. Am. Chem. Soc.* **1997**, *119*, 987.
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