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Intramolecular polar addition reactions of active methylene moieties to aryl-substituted alkenes via photoinduced electron transfer

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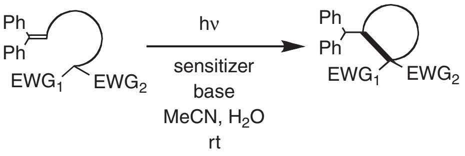
ABSTRACT

The synthesis of cycloalkane derivatives with ring sizes of 5–7 was achieved in moderate yields by photoirradiation of aqueous acetonitrile solutions, containing compounds that consist of active methylene moieties tethered to aryl-substituted alkenes along with sodium hydroxide and 9-cyanophenanthrene. When the substrate contains ethyl cyanoacetate as an asymmetric active methylene moiety, the reaction proceeds in a highly diastereoselective manner.

Ring-forming reactions are among the most interesting transformations in organic chemistry, especially when they are incorporated as key steps in routes for the synthesis of complex natural products. Although numerous methodologies have been developed to generate cyclic structures,[1] additional methods are needed to complement and overcome some potentially weak features of existing procedures.[2]

Several investigations have been carried out thus far to probe the use of intramolecular photochemical polar addition (PPA) reactions as ring-forming processes.[3,4] However, the previous investigations have focused only on substrates that contain carboxy and hydroxy groups as nucleophiles. Cyclization reactions of these types of substrates generate lactones and cyclic ethers. Prior to our current efforts in this area, carbon nucleophiles had not been used in intramolecular PPA reactions to produce carbocyclic-ring systems.[5,6]

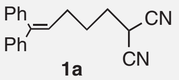
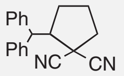
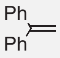
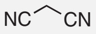
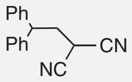
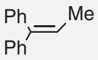
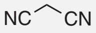
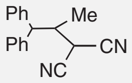
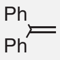
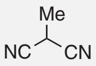
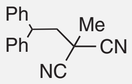
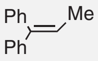
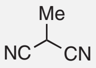
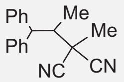
In the study described below, we explored intramolecular versions of PPA reactions of active methylene compounds whose intermolecular counterparts were developed in a recent investigation.[7] These studies have uncovered intramolecular reactions that serve as a facile protocol to construct cycloalkane derivatives under mild conditions (Eq. 1).



(1)

Photoirradiation of an aqueous acetonitrile solution, containing 2-(5,5-diphenylpent-4-enyl)propanedinitrile (**1a**) and 9-cyanophenanthrene (9-CP) in the presence of sodium carbonate, leads to formation of the cyclopentane derivative **4a** in 31% yield (Table 1, entry 1). The corresponding inter-molecular adduct is not produced in this process. The structure of **4a** was determined by using ^{1}H and ^{13}C NMR, MS, HRMS, and IR methods, along with a single-crystal X-ray crystallographic analysis (Fig. S9†). The reaction of **1a** to generate **4a** is the first example of a process that utilizes a

Table 1
Intra- and Inter-molecular PPA reactions[a]

Entry	Substrate(s)		Product	Yield[b] (%)
	Alkene	Propanedinitrile		
1[c]	 **1a**		 **4a**	31
2[d]				66
3[d]				38
4[d]				22
5[d]				0

[a] Conditions: 300-W high-pressure mercury lamp, Pyrex filter, alkene (75 μmol), propanedinitrile (2.5 mmol), 9-CP (25 μmol), Na_2CO_3 (1.25 mmol), in MeCN (4 mL)-H_2O (1 mL), under Ar, rt, 20 h.
[b] Determined by ^{1}H NMR analysis based on the amount of alkene used.
[c] Substrate (**1a**): 75 μmol.
[d] Ref. 7.

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Table 2
Intra-molecular PPA reactions of **1a**, **2a–c**, and **3a**[a]

Entry	Substrate	Base	Product	Yield[b] (%)
1	**1a**	Li_2CO_3	**4a**	18
2	**1a**	Na_2CO_3	**4a**	31
3	**1a**	K_2CO_3	**4a**	36
4	**1a**	Rb_2CO_3	**4a**	42
5	**1a**	Cs_2CO_3	**4a**	56
6	**1a**	NaOH	**4a**	63
7	**1a**	KOH	**4a**	25
8[c]	**1a**	KOBu^t	**4a**	0
9	**2a**	NaOH	**5a**	94
10	**2b**	NaOH	**5b** *epi*-**5b**	33 trace
11	**2c**	NaOH	**5c**	0
12	**3a**	NaOH	**6a**	25

[a] Conditions: 300-W high-pressure mercury lamp, Pyrex filter, substrate (75 μmol), 9-CP (25 μmol), base (1.25 mmol), in MeCN (4 mL)-H_2O (1 mL), under Ar, rt, 20 h.

[b] Determined by ^1H NMR analysis based on the amount of substrate used. Unreacted starting alkenes **1–3** were almost recovered.

[c] In dry MeCN.

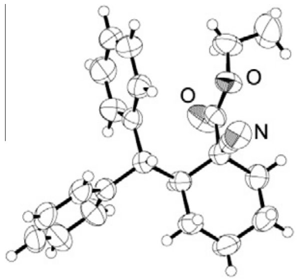
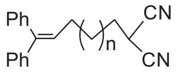
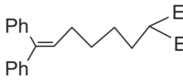


Figure 1. ORTEP diagram for **5b**.

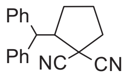
carbon nucleophile in an intramolecular PPA reaction. As such, it represents a mild photochemical carbocyclic-ring forming method.



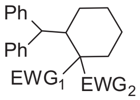
1a ; n = 1
2a ; n = 2
3a ; n = 3



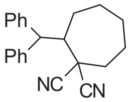
2b ; EWG_1 = CN, EWG_2 = CO_2Et
2c ; EWG_1 = EWG_2 = CO_2Me



4a



5a ; EWG_1 = EWG_2 = CN
5b ; EWG_1 = CN, EWG_2 = CO_2Et
5c ; EWG_1 = EWG_2 = CO_2Me



6a

It is interesting to compare the result of the intramolecular PPA reaction with its intermolecular analogs.[7,8] Inter-molecular photoreaction of 1,1-diphenylethene with propane-dinitrile (malononitrile) affords the PPA adduct in 66% yield (entry 2). The yield of this reaction is lowered when alkene substrates that are sterically hindered at the site of C–C bond formation are employed. A considerable decline in yield is also observed when methyl groups are present in the alkene (entry 3) or propanedinitrile (entry 4) reactants. When both of these substrates contain methyl substituents, PPA reaction does not take place (entry 5). These observations show that the reactivity profiles of the intra- and inter-molecular PPA reactions are contrastingly different (compare entries 1 and 5). This finding indicates that connecting two reacting centers into an intramolecular dyad causes a significant enhancement in the efficiency of the PPA reaction.[3,4]

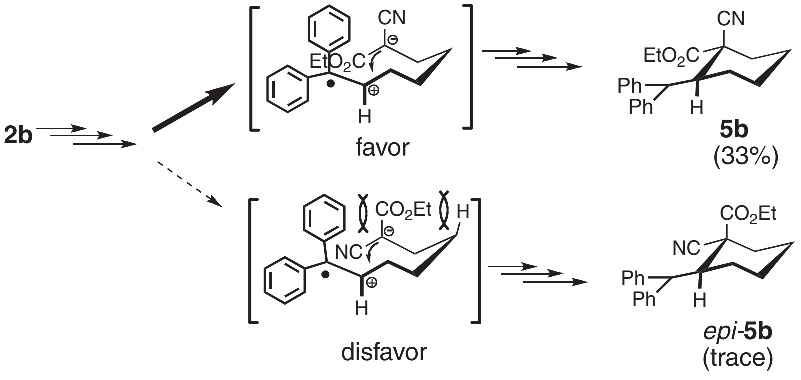
A study of the base dependence of the intramolecular PPA reaction showed that heavier alkali metal carbonates enhance reaction efficiency (Table 2, entries 1–5). The use of sodium hydroxide (entry 6) in contrast to potassium hydroxide (entry 7) affords the best yield of **4a**. Finally, photoproduct **4a** is not formed when potassium *tert*-butoxide is used as the base in dry acetonitrile (entry 8). Other substrates also participate in the intramolecular PPA reaction. For example, the cyclohexane derivative **5a** is generated in high yield (94%) in the intramolecular PPA reaction of the tethered malononitrile **2a** (entry 9 and Fig. S10[†]).

The intramolecular addition of the cyanoacetate-containing substrate **2b** proceeds with high diastereoselectivity. While the major isomer **5b** is formed in 33% yield, only a trace of its epimer *epi*-**5b** can be detected by using GC–MS analysis (entry 10). An X-ray crystallographic analysis revealed that trans relationship exists between the diphenylmethyl and ethoxycarbonyl groups in **5b** and that these groups are located in equatorial positions of the cyclohexane ring (Fig. 1).

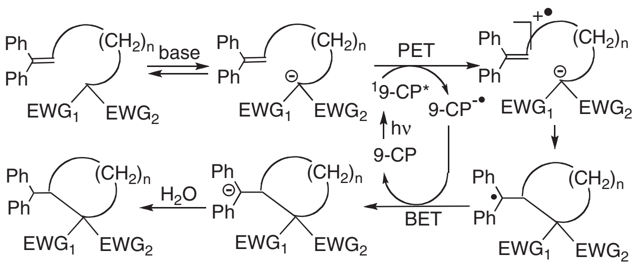
The stereoselectivity of this process can be explained by considering steric interactions that exist between the ethoxy-carbonyl and phenyl groups, and between the ethoxycarbonyl group and a γ-hydrogen atom of the developing six-membered ring (1,3-diaxial interaction) in the transition states for intramolecular addition of the enolate anion to the alkene-derived cation radical (Scheme 1). In fact, these interactions appear to be the cause of the lack of reactivity of the bis(methoxycarbonyl) derivative **2c** (entry 11).

A cycloheptane ring can also be constructed by using intramolecular PPA reaction of **3a**, but the efficiency of this process is not high (entry 12).

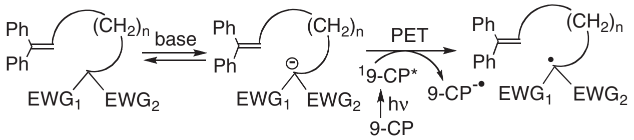
Two mechanisms appear to be plausible for the intra-molecular PPA reaction, both being initiated by deprotonation of the active methylene moieties in substrate **1–3**. One, following the normal PPA pathway (Scheme 2),[7–10] involves photoinduced electron transfer (PET) from the alkene moiety to the excited singlet state of 9-CP (^{1}9-CP*) to afford an intramolecular radical cation–anion



Scheme 1. Steric relationship around the reaction site of **2b**-derived intermediate.



Scheme 2. Plausible mechanism (Path I): PET from the alkene moeity.



Scheme 3. Plausible mechanism (Path II): PET from the anion of active methylene moeity.

pair. Nucleophilic addition of the anion moiety to the radical cation moiety then takes place to form a cyclic radical intermediate that accepts an electron from 9-CP$^{\cdot-}$ (back electron transfer; BET) to form an anion which is protonated to form the carbocyclic product. An alternative route resembles the mechanism for radical cyclization (Scheme 3). In it, PET occurs from the anion of active methylene moiety to the excited state of the sensitizer to yield a radical that undergoes intramolecular addition to the alkene to afford the same cyclic radical that serves as an intermediate in the other mechanistic pathway. Since both PET pathways should be highly exergonic ($\Delta G_{\text{et}} = -0.98$ and -2.96 eV when **1a** is used)[11–13] and both cyclization steps should take place smoothly, it is possible that both are involved in this novel cyclization process.

In conclusion, a novel and facile synthetic method for the construction of cycloalkane derivatives that relies on intramolecular PPA or radical cyclization reactions of active methylene compounds tethered to aryl-substituted alkenes has been developed in this effort. When ethyl cyanoacetate is used as a pro-asymmetric active methylene moiety, the reaction proceeds with a high degree of diastereoselectivity. Moreover, the study has uncovered the first examples in which carbon nucleophiles are employed in intramolecular PPA reactions.

Finally, the new process might be synthetically useful since it proceeds under relatively mild conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2010.07.165.

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11. Oxidation potentials of **3a** and $(NC)_2CH^-$ are +1.66 V and +0.55 V[12] versus SCE, and the reduction potential of 9-CP is −0.87 V versus SCE. Excited singlet state energy of 9-CP is 3.45 eV. ΔG_{et} values were calculated by use of Rehm–Weller equation (see Ref. 13).
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