Ambiphilic Allenes: Synthesis and Reactivity[†]

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Received (in XXX, XXX) Xth XXXXXXXXXX 200X, Accepted Xth XXXXXXXXXX 200X

First published on the web Xth XXXXXXXXXX 200X

DOI: 10.1039/b000000x

Ambiphilic allenes are generated by an organocatalyzed domino reaction of alkyl propiolates and aromatic 1,2-diketones. In the absence of any external chemical agent, these allenes perform a thermally-driven dimerization reaction to generate the corresponding fully-substituted cyclobutanes in a regio- and highly stereoselective manner.

The search for organic molecules expressing ambiphilic reactivity is a sought-after challenge in organic chemistry.¹ Isocyanides constitute a paradigmatic example with a carbon atom able to react with both electrophiles and nucleophiles.² Allenes armed with an e-donating group and an e-acceptor group at the C3- π system (1,3-relationship) are expected to express this property at C2 position (Figure 1). Allene reactivity is regulated to a large extent by the substitution pattern adorning the C3- π system.³ On this sense, although the

Figure 1. Substituent effect on the allene reactivity.

individual effect of e-donating (EDG) and e-withdrawing groups (EWG) on the allene reactivity are well established (Figure 1),^{3a,4} the overall effect when they operate in a 1,3-
assonant manner remains to be evaluated. With these precedents we have initiated a research program aimed to the synthesis and the study of 1,3-bifunctional allenes as synthetically relevant ambiphilic reactants for the

development of novel domino and multicomponent reactions. For experimental reasons related to our previous work on the chemistry of non-metallic conjugated acetylides,⁵ we selected the allenic esters **1** as the target bifunctional allene for these studies.⁶

We envisioned that these allenic esters could be synthesized by a tertiary amine-catalyzed domino reaction involving 1,2-diketones and terminal conjugated acetylides (Scheme 1). The manifold was devised on the basis of our previous studies on the organocatalyzed generation of conjugated acetylides **I** and their reactivity against different types of electrophiles.⁷ It was hypothesized that the intermediate **II**, obtained from the nucleophilic addition of **I** onto the 1,2-diketone, should suffer a rearrangement that would lead to the rupture of the more labile CO-CO bond (BE $\approx$ 70 Kcal/mol) via epoxide **III**.⁸ Interestingly, and in accordance with our previous experiences, in the process to form the desired allene **1**, intermediate **IV** would be basic enough to generate more acetylide and regenerate the nucleophile from its β -ammonium acrylate resting state, and thus, keep the catalytic cycle going.

Scheme 1. Tertiary amine-catalyzed domino-based manifold

To test this proposal, we chose the Et₃N-catalyzed reaction

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[†]Electronic supplementary information (ESI) available: Experimental section and physical data for compounds **4-9**. CCDC reference numbers 704023 and 704024. For ESI and crystallographic data in CIF see DOI: 10.1039/b000000x

of benzil (**2a**) and methyl propiolate (**3a**) as the model reaction (Scheme 2). It was found that when a solution of both reactants in dichloromethane was treated at 0°C with Et₃N (10 mol%), a smooth reaction occurred affording a major product which slowly transformed into other products. Interestingly, this intermediate could be detected by TLC but it could not be isolated for characterization. A more detailed study of the reaction showed that after 10 min at 0°C the practical totality of the starting benzil had been transformed into this new compound. Quenching the reaction at this time with pyrrolidine afforded enamine **4** (77%) which could be isolated and further hydrolyzed to ketone **5**. Because enamine **4** is the expected addition compound on an allene such as **1aa**, we assigned this structure to the main reaction intermediate, thus verifying the postulated cascade of events shown in Scheme 1. This assignment was further corroborated by running the reaction in an NMR tube using CDCl₃ as solvent. ¹³CNMR analysis of the reaction mixture at different times showed that the quaternary allene peak at 210 ppm,^{6c} clearly visible just 20 minutes after setting the reaction, totally disappeared when the reaction was completed. In a separate experiment, the reaction mixture was allowed to progress overnight at room temperature and under these conditions, allene **1aa** was fully transformed into the mixture of cyclobutanes **6aa-7aa** and cyclobutene **8aa** (75%) (Scheme 2). Prolonged treatment of this mixture with Et₃N (1 equiv; 24 h) generated the mixture of cyclobutanes **6aa** and cyclobutenes **8aa** via quantitative transformation of **7aa** into **8aa**. Structures of cyclobutane **6aa** and cyclobutene **8aa** were unambiguously confirmed by X-ray crystallographic analyses.⁸ To the best of our knowledge, this

protocol constitutes the first example of a synthesis of allenes involving a rearrangement of 1,2-diarylketones.

Cyclobutanes **6aa** and **7aa** constitute therefore the chemical picture of the allene's basal reactivity which is expressed as a stereoselective and self-biased formal [2+2]-cycloaddition. Due to the novelty and functional complexity of these cyclobutanic products, we undertook a study of the synthetic scope of this transformation (Table 1). The reaction proved to be general with regard to both the alkyl propiolate (entries 1-5) and the electronic nature of the aromatic 1,2-diketones (entries 1, 6-10) affording a combined yield of cyclic products **6** and **8** typically in 60-75% yield. Although relatively small amounts of 1,2-diketone starting materials were always recovered, use of excess propiolate did not increase the conversion. In all of the cases, cyclobutanes **6** were obtained as the major products with an impressive high *trans*-diastereoselectivity (more interesting C₂-symmetry), while minor cyclobutenes **8** are generated as single geometric isomers. The regioselectivity of the formal [2+2]-cycloaddition is moderate and it remains practically unchanged in the -78° to 20°C temperature range. Finally and not less important for practical purposes, the reaction could be easily scaled up to 100 mmol with a similar chemical efficiency (68% of combined yield) (Entry 2).

Table 1. Et₃N-catalyzed reaction of 1,2-diketones **2** with alkynoates **3**.^{a,†}

Entry	2	Ar= R-C ₆ H ₄ -	3	6 (dr) ^a	8	Rsm ^b
1	a	H	a Me	51 (97:3)	24	10
2	a	H	a Me	47 (97:3) ^c	21	
3	a	H	b Et	48 (96:4)	21	13
4	a	H	c <i>t</i> Bu	40 (9:1)	28	23
5	a	H	d Bn	43 (97:3)	20	22
6	b	4-Me	a Me	51 (97:3)	20	13
7	c	4-F	a “	55 (≥99)	17	14
8	d	4-MeO	a “	50 (97:3)	14	24
9	e	3-MeO	a “	42 (96:4)	18	14
10	f	(2-furylCO) ₂	a “	22 (≥99)	6	20

^a *Trans:cis* ratio determined by integration of representative ¹HNMR signals. ^b Recovered 1,2-diketone. ^c 100 mmol scale.

Scheme 2. Et₃N-catalyzed reaction of benzil and methyl propiolate.

Cyclic acenaphthenequinone **2g** afforded spiro-1,3-dioxolane derivatives **9** and a small amount of **6ga** (Scheme 3). Observe that in this case, the CO-CO σ-bond is strong enough to inhibit the rearrangement and the transformation is funnelled toward the 1,3-dioxolane **9** formation through an ABB' 3CR acetylide-driven process.⁷ When fixing the stoichiometry to that required for the ABB' 3CR process (2:1), the yield of **9** goes up to 70% (mixture of isomers) and **6ag** is not produced.

Scheme 3. Acetylide-driven 1,3-dioxolane **9** formation.

A preliminary DFT study at the B3LYP/6-31G* level showed a HOMO-LUMO gap of 0.17030 eV for allene **1aa**, a magnitude sufficiently small to allow an ambiphilic reactivity profile (Table 2).⁹ This property also explains the observed smooth tendency for dimerization and the complete observed regioselectivity. Table 2 highlights the activating effect exercised by both the Ph and OBz groups allocated at C₃ and the opposite effect played by the ester group at C₁. Although a widely accepted stepwise mechanism involving a perpendicular bisallyl diradical¹⁰ would explain the observed regio- and stereoselectivity, a concerted mechanism cannot be ruled out.¹¹

Table 2. HOMO-LUMO energies (eV) for R¹R²C=C=CR³

R ¹	R ²	R ³	HOMO	LUMO	ΔE
H	H	H	-0.26297	0.02065	0.28362
Ph	H	H	-0.21846	-0.02670	0.19176
OBz	H	H	-0.24221	-0.05275	0.18946
H	H	CO ₂ Me	-0.26746	-0.03807	0.22939
Ph	OBz	H	-0.21814	-0.04983	0.16831
Ph	OBz	CO ₂ Me	-0.22733	-0.05703	0.17030

In summary, we have reported a novel and efficient organocatalytic synthetic manifold to gain access to bifunctional allenes **1** from readily available starting materials, under mild reaction conditions and in very short periods of times. In the absence of other chemical reactants, these allenes suffer a remarkably smooth thermally-driven dimerization to form the functionalized complex cyclobutanes **6** and cyclobutenes **8**. Overall, the reaction mainly generates one C₂-symmetric cyclobutane ring featuring two quaternary aromatic esters, two exocyclic conjugated aliphatic esters, and thus, a (Z,Z)-1,3-diene function. Interestingly, the reaction network forms two C-O and four C-C bonds, while only breaks two C-C bonds. Finally, and not less important, the in situ generation of these allenes is mild enough to be compatible with a large number of organic functionalities and it constitutes an excellent workbench for the discovery of new complexity generating processes. The efficient formation of enamine **4** is a good example of this property. This issue is being developed in our lab.

Acknowledgements. This work was supported by the Spanish

Ministerio de Educación y Ciencia and the European Regional Development Fund (CTQ2005-09074-C02-02), the Spanish MSC ISCI (RETICS RD06/0020/1046), CSIC (Proyecto Intramural Especial 200719) and Fundación Instituto Canario de Investigación del Cáncer (FICI-G.I.N°08/2007). Authors thank technicians Sonia Rodríguez Díaz and Aida Sánchez López for preparative work.

Notes and references

- ‡ **Representative procedure:** 1,2-Diketone **2a** (3.00 mmol) and methyl propiolate (**3a**) (3.00 mmol) are dissolved in CH₂Cl₂ (5 mL) and the solution is cooled to 0°C in an ice bath. Et₃N (0.30 mmol) is added and the reaction is allowed to react overnight without further cooling. Et₃N (3 mmol) is added and the reaction is allowed to react for one additional day (this step simplifies the isolation of **6aa** while transforms **7aa** cis/trans into **8aa**). Purification of products **6aa** trans/cis and **8aa** was carried out by flash column chromatography (silica gel, n-hexane/EtOAc 80/20 to 60/40). **Cyclobutane 6aa** trans-isomer (major): White solid, m.p. = 181.0-182.6°C; ¹H NMR (400 MHz, CDCl₃, 25°C): δ = 3.37 (s, 6H), 6.86 (s, 2H), 7.16-7.29 (m, 10H), 7.41 (tt, *J* = 7.4 and 1.3 Hz, 2H) 7.56 (m, 4H), 7.69 (m, 4H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = □□51.5, 92.4, 117.8, 127.6, 128.0, 128.1, 128.2, 129.2, 129.9, 132.5, 134.8, 151.2, 163.3, 164.7; IR (HCCl₃): ν = 3027.8, 1730.3, 1449.9, 1436.1, 1343.8, 1268.1, 1222.3, 1108.6 cm⁻¹; Anal. Calcd. for C₃₆H₂₈O₈: C, 73.46; H, 4.79. Found: C, 73.47; H, 4.71; m/z (%): 588 (0.3) [M⁺], 362 (8.4), 162 (28), 130 (19), 105 (100), 77 (32). **Cyclobutene 8aa**: Yellow solid, m.p. = 156.5-157.9°C; ¹H NMR (400 MHz, CDCl₃, 25°C): δ = 3.32 (s, 3H), 3.38 (s, 3H), 6.08 (s, 1H), 7.33-7.41 (m, 6H), 7.46-7.54 (m, 6H), 7.65 (tt, *J* = 7.5 and 1.3 Hz, 2H), 8.19 (m, 2H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = 51.0, 51.5, 110.4, 126.5, 127.5, 127.9, 128.0, 128.6, 128.77, 128.79, 129.0, 129.5, 130.1, 131.1, 133.9, 134.4, 136.5, 142.2, 149.5, 156.6, 161.5, 164.6, 165.4; IR (HCCl₃): ν = 3028.2, 2953.0, 1731.6, 1435.9, 1258.0, 1063.4 cm⁻¹; Anal. Calcd. for C₂₉H₂₂O₆: C, 74.67; H, 4.75. Found: C, 74.77; H, 5.00; m/z (%): 466 (24) [M⁺], 330 (10), 215 (17), 106 (19), 105 (100), 77 (60).
- § **Crystal data** for **6aa**: C₃₆H₂₈O₈, *M* = 588.58, monoclinic, *a* = 31.764(3), *b* = 10.8730(10), *c* = 18.823(2) Å, β = 91.707(5)°, *V* = 6498.0(11) Å³, *T* = 293K, space group C2/c (no. 15), *Z* = 8, 34744 reflections measured, 5184 unique (*R*_{int} = 0.064). All non-hydrogen atoms were refined with anisotropic thermal parameters using full-matrix least squares procedures on *F*². The solvent molecule (dichloromethane) presented a higher disorder and it was impossible to establish a good model even using an isotropic refinement. Therefore a SQUEZZE procedure was made in order to eliminate the contribution of the solvent molecule. In any case it does not play an important role in the structure. All H atoms were placed in geometrically calculated positions. The methyl-H atoms were refined as rigid groups, which were allowed to rotate but not to tip, with *U*_{iso}(H) = 1.5*U*_{eq}(C). All other H atoms were allowed to ride on their parent atoms with *U*_{iso}(H) = 1.2*U*_{eq}(C). The final *R* and *wR*² were 0.0770 and 0.2019 respectively. CCDC 704023. **Crystal data** for **8aa**: C₂₉H₂₂O₆, *M* = 466.47, monoclinic, *a* = 10.769(1), *b* = 9.678(1), *c* = 23.311(1) Å, β = 96.400(2)°, *V* = 2414.4(4) Å³, *T* = 293K, space group P21/c (no. 14), *Z* = 4, 27643 reflections measured, 3454 unique (*R*_{int} = 0.047). Only the reflections up to 0.9 Å were considered in the refinement process. All non-hydrogen atoms were refined with anisotropic thermal parameters using full-matrix least squares procedures on *F*². The molecule presents a moderate disorder in one carboxylic group (O4-C20-O3-C21) that was modeled using two sites with occupancy levels of 70% and 30% of probability. All H atoms were placed in geometrically calculated positions. The methyl-H atoms were refined as rigid groups, which were allowed to rotate but not to tip, with *U*_{iso}(H) = 1.5*U*_{eq}(C). All other H atoms were

allowed to ride on their parent atoms with $U_{\text{iso}}(\text{H})=1.2U_{\text{eq}}(\text{C})$. The final R and wR^2 were 0.0699 and 0.1955 respectively. CCDC 704024.

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