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Regio- and Stereoselectivity in the 1,3-Dipolar Cycloaddition Reactions of Isoquinolinium Ylides with Cyclopenta[*a*]acenaphthylen-8-ones

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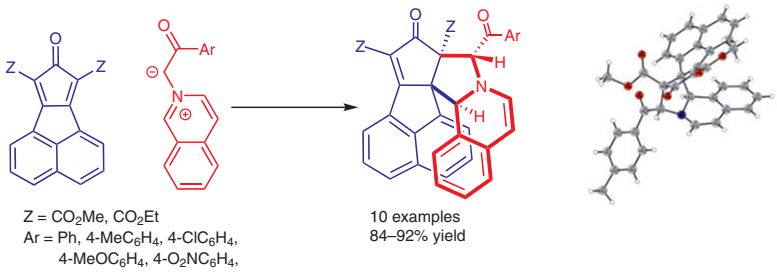

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Abstract A convenient regio- and diastereoselective synthesis of functionalized 5a,5b-dihydro-5*H*,13*H*-naphtho[1′′,8′′:4′,5′,6′]pentaleno[1′:3,4]pyrrolo[2,1-*a*]isoquinolin-5-ones via 1,3-dipolar cycloaddition reaction of 8*H*-cyclopenta[a]acenaphthylen-8-ones with carbonyl-stabilized isoquinolinium *N*-ylides, is described. Based on DFT calculations at b3lyp/6-311+g(d,p) level of theory, a nonconcerted mechanism is proposed to explain the regioselectivity of this reaction. The structure of a typical product was confirmed by X-ray crystallographic analysis.

Key words regioselective synthesis, 1,3-dipolar cycloaddition, isoquinolinium ylide, cyclopentadienones, DFT calculations

Cyclopentadienone (**1**) represents an unusual system of crossed conjugated double bonds in a five-membered ring.[1] Cyclopentadienones are antiaromatic dienes having low HOMO–LUMO energy gaps.[2] Although **1** and nearly all of the simple cyclopentadienones that have been prepared are dimeric, tetraarylcyclopentadienones **2** and fused-ring cyclopentadienones, such as disubstituted 8*H*-cyclopent[*a*]acenaphthylen-8-ones (**3** and **4**), are monomeric (Figure 1).[3] The factors that determine whether a monomer or a dimer is formed appear to be steric in nature. All of the monomeric cyclopentadienones are colored and many have been studied for the effect of substituents and fused rings on the ultraviolet and visible absorption.[4] The tetraaryl derivatives **2** are powerful dienes in a Diels–Alder reaction and have been used for the synthesis of highly arylated compounds.[5] With alkenes or alkynes the reaction can lead to the formation of bridged carbonyl compounds, which can lose carbon monoxide upon heating. The catalytic reactivity of iron cyclopentadienone complexes have been reported.[6] The synthesis, reactions, and physical properties of cyclopentadienones have been extensively reviewed.[3]

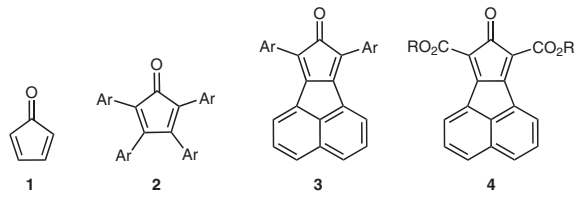
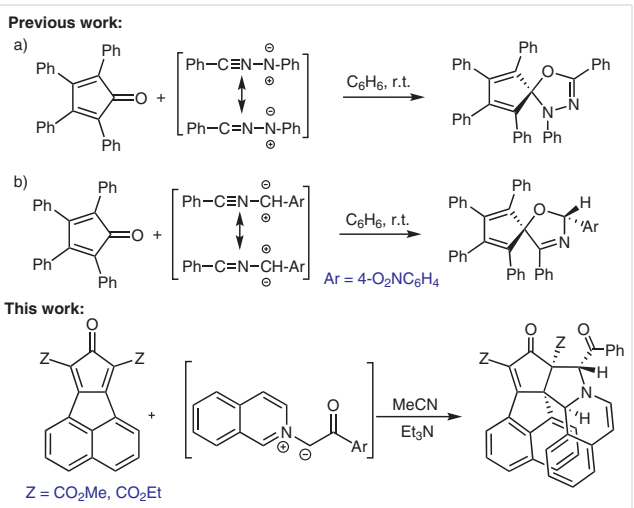


Figure 1 Cyclopentadienone and its monomeric derivatives

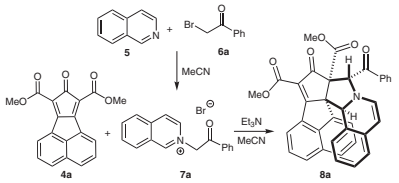
The cyclopentadienone system has been proved to be a privileged and peculiar dipolarophile. Thus, in the cycloaddition of tetrasubstituted cyclopentadienones with nitrile oxides, the 1,3-dipole attacks the ring C=C double bond,[7a] whereas with nitrile imines[7b] and nitrile ylides,[7c] the dipole attacks the carbonyl double bond (Scheme 1). It was of interest, therefore, to study the cycloaddition of the ring-fused 7,9-bis(alkoxycabonyl)-8*H*-cyclopent[*a*]acenaphthylen-8-ones[8] with carbonyl-stabilized isoquinolinium ylides,[9] to examine the position of attack by this dipole and the regioselectivity of the cycloadducts. As shown in Scheme 1, the 1,3-dipole attacks the ethylene double bond of cyclopentadienone derivative to afford a heptacyclic adduct.



Scheme 1 Dipolar cycloaddition of fused cyclopentadienones with: a) diphenylnitrilimine, b) benzonitrile-4-nitrobenzylide, and carbonyl-stabilized isoquinolinium ylide.

Initially, the reaction between 7,9-bis(methoxycabonyl)-8*H*-cyclopent[*a*]acenaphthylen-8-one (**4a**) and 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide (**7a**), prepared in situ from isoquinoline (**5**) and phenacyl bromide (**6a**), was investigated in the presence of Et_3N. The reaction proceeded smoothly in MeCN at room temperature (25 °C) and afforded dimethyl 4-benzoyl-5-oxo-4*H*,12c*H*-naphtho[1″,8″:4′,5′,6′]pentaleno[1′:3,4]pyrrolo[2,1-*a*]isoquinoline-4a,6(5*H*)-dicarboxylate (**8a**) in 80% yield (Table 1). In order to optimize the reaction conditions for the formation of **8a**, the effects of solvent and temperature were studied. As shown in Table 1, H_2O, MeOH, DMF, MeCN, and CH_2Cl_2 were examined. Ultimately, MeCN was found to be the best solvent at 80 °C.

Table 1 Optimization of Reaction Conditions for the Formation of **8a**[a]

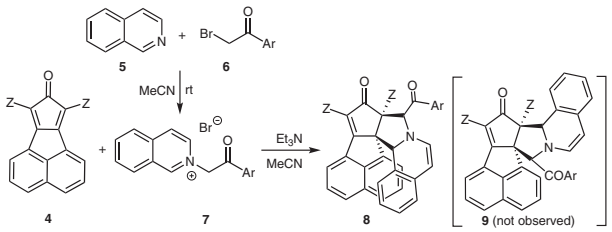


Entry	Solvent	Temp (°C)	Yield (%)[b]
1	H_2O	60	trace
2	MeOH	60	15
3	CH_2Cl_2	25	50
4	DMF	25	20
5	MeCN	25	80
6	MeCN	80	86

[a] Reaction conditions: **4a** (1.0 mmol), 7a (1.0 mmol), Et_3N (1.0 mmol), solvent (6 mL), 2 h.
[b] Yield of isolated product.

To determine the scope of this approach, a number of phenacyl bromides **6** were tested under the reaction conditions. As shown in Table 2, phenacyl bromides bearing electron-donating or electron-withdrawing substituents provided the functionalized pyrrolo[2,1-*a*]isoquinoline derivatives **8** in good yields (84–92%).[10]

Table 2 Synthesis of Fused Pyrrolo[2,1-*a*]isoquinolines **8**[a]



Entry	Z	Ar	Product **8**	Yield (%)[b]
1	CO_2Me	Ph	**8a**	86
2	CO_2Et	Ph	**8b**	88
3	CO_2Me	4-ClC_6H_4	**8c**	85
4	CO_2Et	4-ClC_6H_4	**8d**	90
5	CO_2Me	4-MeC_6H_4	**8e**	87
6	CO_2Et	4-MeC_6H_4	**8f**	86
7	CO_2Me	4-$MeOC_6H_4$	**8g**	92
8	CO_2Et	4-$MeOC_6H_4$	**8h**	85
9	CO_2Me	4-$O_2NC_6H_4$	**8i**	90
10	CO_2Et	4-$O_2NC_6H_4$	**8j**	84

[a] Reaction conditions: **4** (1 mmol), **7** (1 mmol), Et_3N (1 mmol), solvent (6 mL).
[b] Isolated yield.

The structures of products **8a–j** were elucidated by ^1H NMR, ^{13}C NMR, IR, and mass spectral data. The ^1H NMR spectrum of **8a** exhibited four sharp singlets for the methoxy (δ = 3.51 and 3.86 ppm) and methine (δ = 4.82 and 6.13 ppm) protons. The aromatic protons show characteristic multiplets (δ = 6.37–8.27 ppm) in the spectrum. The ^{13}C NMR spectrum of **8a** showed 34 signals in agreement with the proposed structure. The mass spectrum of **8a** displayed the molecular ion peak at *m/z* = 567. The NMR spectra of compounds **8b–j** were similar to those of **8a**, except for the substituents, respectively.

Clear evidence for the structure of **8e** was obtained from single-crystal X-ray analysis.[11] The ORTEP diagram of **8e** is shown in Figure 2. There are eight molecules of **8e** in the unit cell, which are arranged in a centrosymmetric manner. The structure obtained from the crystallographic data, and those of **8a–d** and **8f–j** were assumed to be analogous on account of their similar NMR spectra.

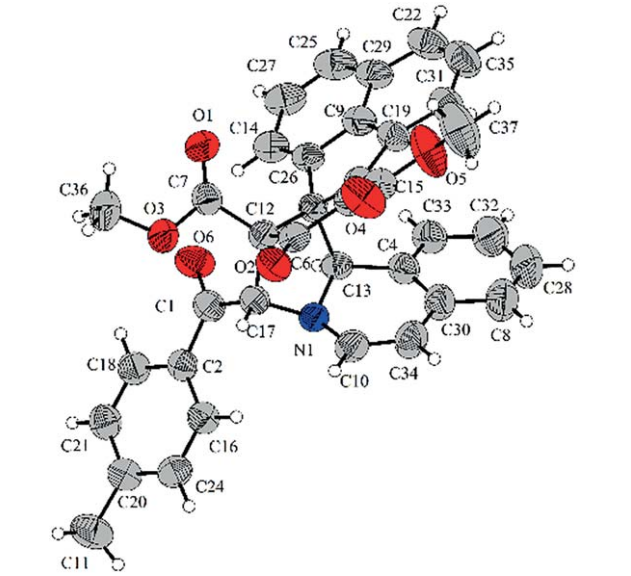


Figure 2 X-ray crystal structure of compound **8e**

The ^{13}C NMR spectra of compounds **8a–j** showed five signals above δ = 160 ppm. Two of these signals which appear between δ = 160–170 ppm are assigned to the ester C=O groups, and two of the remaining peaks appearing above δ = 190 ppm are attributed to the ketone carbonyl groups. In order to assign the last signal appearing above δ = 190 ppm, we turned to DFT calculations at the b3lyp/6-311+g(d,p) level of theory.[12] Thus, the NMR calculations performed to estimate the chemical shifts of the five ^{13}C signals in compound **8e** that appear above δ = 160 ppm are shown in Figure 3.

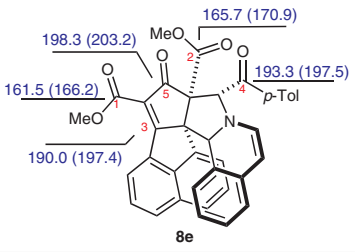


Figure 3 Comparison of the experimental (and theoretical) values of ^{13}C NMR chemical shifts (in ppm) for the five low-field signals (between δ = 160–200 ppm) observed in the ^{13}C NMR spectrum of compound **8e**

The frontier molecular orbital diagram for carbonyl-stabilized isoquinolinium ylide **10** and cyclopentadienone **4** is shown in Figure 4. The HOMO–LUMO energy levels are given in eV. According to this diagram, the dipolar cycloaddition reaction between **4** and **10** is controlled by the orbital energy of isoquinolinium ylides.[13]

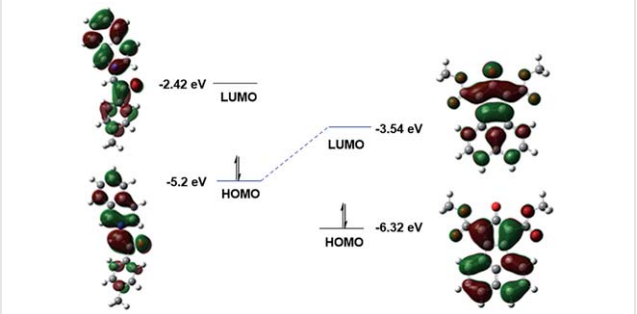


Figure 4 Frontier orbital diagram for isoquinolinium ylides **10** (left) and cyclopentadienone **4** (right). The HOMO–LUMO energy levels are given in eV.

DFT has been accepted by chemists as a reliable approach for computation of molecular structures and energies of chemical systems.[14] To estimate the molecular reactivities of **4** and **10**, the values of global chemical reactivity descriptors such as electronic chemical potentials (μ),[15] chemical hardness (η),[16] and electrophilicity (ω)[17] for reactants **4** and **10** are calculated by this method. As shown in Table 3, the chemical hardness for the reactants is almost the same, but the electronic chemical potential value of **10** is higher than that of **4**. Therefore, charge transfer is expected to take place from isoquinolinium ylide **10** to **4**. Also, the comparison of the nucleophilicity and the electrophilicity of the reactants showed that the dipolar species **10** would act as the nucleophile in this cycloaddition reaction.

Table 3 Frontier MO Energies and Reactivity Descriptors for Reactants **4** and **10** Calculated at the b3lyp/6-311+G(d,p) Level of Theory[a]

Comp	E_{HOMO}	E_{LUMO}	μ	η	N	ω
10	–5.20	–2.42	–3.80	1.395	4.24	5.19
4	–6.32	–3.54	–4.93	1.390	3.17	8.74

[a] All energetics are given in eV.

A DFT diagram for mechanistic rationalization of the regioselective nonconcerted formation of product **8** is given in Figure 5. It is presumed that initially the reaction of isoquinoline (**5**) and phenacyl bromide (**6a**) generates the isoquinolinium salt (**7**), which is converted into the isoquinolinium ylide (**10**) by Et_3N. A nonconcerted regioselective addition reaction occurs between the electron deficient C2–C3 π bond of cyclopentadienone and the isoquinolinium ylide to afford the zwitterionic intermediate **11**. This intermediate is converted into the heptacyclic pyrrolo[2,1-*a*]isoquinoline **8**.

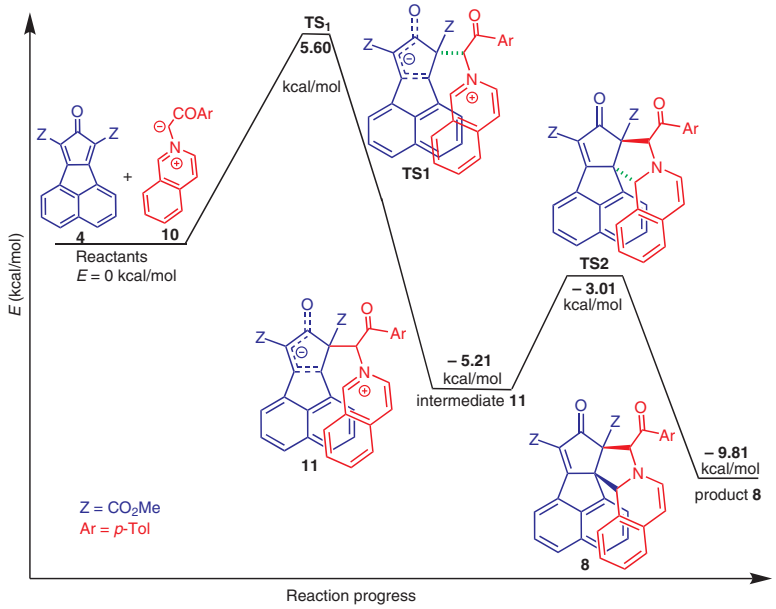


Figure 5 DFT diagram for mechanistic rationalization of the regioselective nonconcerted formation of product **8**. Relative energies (Δ*E*) for cycloaddition reaction are calculated according to reactants whose *E* = –1932.777495 Hartree at b3lyp/6-311+G(d,p) level of theory.

In summary, we have developed a regio- and diastereoselective synthesis of functionalized 5a,5b-dihydro-5*H*,13*H*-naphtho[1″,8″:4′,5′,6′]pentaleno[1′:3,4]pyrrolo[2,1-*a*]-isoquinolin-5-ones via 1,3-dipolar cycloaddition of 7,9-bis(alkoxycabonyl)-8*H*-cyclopent[*a*]acenaphthylen-8-ones with carbonyl-stabilized isoquinolinium ylides, derived from isoquinoline and phenacyl bromides in the presence of Et_3N in MeCN. Based on DFT calculations at b3lyp/6-311+g(d,p) level of theory, a nonconcerted mechanism is proposed to explain the selectivity of this reaction. The methodology reported here may serve as a convenient strategy to create a wide range of functionalized heptacyclic pyrrolo[2,1-*a*]isoquinoline derivatives.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706750.

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(10) **Typical Procedure for the Preparation of 8**
To a stirred mixture of N-substituted isoquinolinium salts **7** (1.0 mmol) and Et_3N (1.1 mmol) in MeCN (6.0 mL) was added cyclopentadienone **4** (1 mmol),[9a] and the resulting mixture was stirred at 80 °C for 3 h. After completion of the reaction (TLC monitoring), the mixture was filtered, and the precipitate was washed with cold MeCN and *n*-hexane to afford the products **8a–j**.
Dimethyl 4-Benzoyl-5-oxo-4*H*,12c*H*-naphtho-[1″,8″:4′,5′,6′]-pentaleno[1′:3,4]pyrrolo[2,1-*a*]isoquinoline-4a,6(5*H*)-dicarboxylate (8a)
Orange crystals; yield 0.487 g (86%); mp 224–225 °C. IR (KBr): 3061, 2976, 1742, 1730, 1680, 1608, 1020 cm^{-1}. ^1H NMR: δ = 3.51 (s, 3 H), 3.86 (s, 3 H), 4.82 (d, *J* = 7.3 Hz, 1 H), 4.93 (s, 1 H), 5.26 (d, *J* = 7.3 Hz, 1 H), 6.07 (t, *J* = 7.3 Hz, 1 H), 6.13 (s, 1 H), 6.37 (d, *J* = 7.5 Hz, 1 H), 6.75 (d, *J* = 7.3 Hz, 1 H), 6.83 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.0 Hz, 1 H), 7.56 (t, *J* = 7.0 Hz, 1 H), 7.62 (d, *J* = 7.0 Hz, 2 H), 7.78 (d, *J* = 7.0 Hz, 1 H), 7.84 (t, *J* = 8.0 Hz, 1 H), 8.00 (t, *J* = 8.0 Hz, 2 H), 8.15 (d, *J* = 8.0 Hz, 2 H), 8.27 (d, *J* = 7.0 Hz, 1 H). ^{13}C NMR: δ = 52.0 (MeO), 52.6 (MeO), 71.7 (CH), 73.1 (C), 73.7 (CH),

75.0 (C), 103.0 (CH), 121.7 (CH), 123.4 (C) 124.3 (CH), 124.5 (2 CH), 124.8 (C), 125.7 (CH), 126.1 (CH), 127.9 (CH), 128.2 (CH), 128.8 (2 CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 130.6 (C), 130.7 (C), 131.0 (CH), 132.2 (C), 133.8 (CH), 135.3 (C), 135.4 (CH), 139.1 (C), 141.9 (C), 161.5 (C = O), 165.7 (C = O), 190.0 (C), 193.7 (C = O), 198.2 (C = O). MS (EI, 70 eV): *m/z* (%) = 567 (4) [M$^+$], 437 (50), 338 (31), 301 (54), 279 (36), 244 (45), 203 (18), 187 (27), 105 (100). Anal. Calcd for $C_{36}H_{25}NO_6$ (567.60): C, 76.18; H, 4.44; N, 2.47. Found: C, 75.88; H, 4.46; N, 2.46.

(11) **X-ray Crystal-Structure Determination of 8e**
CCDC 1969492 contains the supplementary crystallographic data for this paper (structure **8e**). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(12) (a) Calculations
All calculations in this paper were carried out with Gaussian 09 package12a by using the DFT method. Through the comparison of theoretical and experimental data, obtained from X-ray crystallography, we found that b3lyp/6-311+g(d,p)12b,c results were in best agreement with the experimental data. These comparisons were based on bond lengths, bond angles, and dihedral angles. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J.; Klene, M. M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 09, Revision A.02. 2016. (b) Johnson, B. G.; Fisch, M. J. *J. Chem. Phys.* **1994**, *100*, 7429. (c) Gauss, J. *J. Chem. Phys.* **1993**, *99*, 3629.

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