Unprecedented Regio- and Stereoselective Synthesis of Pyrene-Grafted Dispiro[indoline-3,2′-pyrrolidine-3′,3″-indolines]: Expedient Experimental and Theoretical Insights into Polar [3 + 2] Cycloaddition

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ABSTRACT: A series of dispiro[indoline-3,2′-pyrrolidine-3′,3″-indolines] was synthesized via a multicomponent polar [3 + 2] cycloaddition (32CA) reaction of isatin derivatives, sarcosine and (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-one derivatives. The regio- and stereochemistries of the cycloadducts were established on the basis of one-dimensional (1D) (1H-, 13C-, 13C-CRAPT NMR) and two-dimensional (2D) homonuclear and heteronuclear correlation NMR spectrometry experiments (1H−1H gDQFCOSY, 13C−1H-HSQCAD, 13C−1H-HMBCAD, 1H−1H-ROESYAD). The molecular mechanism and regio- and stereoselectivities of the cycloaddition (CA) reaction have been investigated utilizing a density functional theory (DFT) method and were thoroughly explained based on the transition-state stabilities and global/local electrophilicity/nucleophilicity reactivity indices of the reactants.

INTRODUCTION

Pyrene is a prominent polynuclear aromatic hydrocarbon and is considered to be one of the most useful skeletons for the construction of fluorogenic chemosensors for a variety of important chemical species.1 In the past several decades, synthesis of pyrrolidine-based heterocycles has been a major source of attraction because they comprise an important class of substances with highly pronounced biological activities, and the pyrrolidine moiety is also the core skeleton of numerous alkaloids.2 Multicomponent [3 + 2] cycloaddition (32CA) reactions are incredibly useful reactions for the synthesis of five-membered heterocycles, usually in a high regio- and stereoselective manner.3 Consequently, polar 32CA of azomethine ylides [generated by the reaction of α-amino acids and carbonyl compounds] to electron-deficient alkenes is considered as one of the most expedient and efficient synthetic protocols for the construction of highly functionalized five-membered heterocycles such as the pyrrolidine ring.4 Moreover, spiropyrrrolidine-oxindole derivatives exhibit promising biological applications prospects based on their reported antibiotic, antidiabetic, anticonvulsant, antiviral, antibacterial, anti-inflammatory, antitubercular, and anticancer activities.3 In addition to the selectivity behavior, the understanding of the fundamental principles in the polar 32CA reactions has been gradually developed from prolific studies of the interplay between experimental and theoretical aspects, and it still remains a formidable challenge.5 The steric and electronic effects are two key factors that can impact the regio- and stereoselectivities of these reactions.7 Their regio- and stereochemistries may be controlled either by selecting the appropriate dipole and/or dipolarophile or by conducting the reaction using a catalyst.8

Furthermore, the molecular mechanism and the origins of the regio- and chemoselectivities in 32CA reactions have been theoretically studied based on density functional theory (DFT) reactivity indices9 and molecular electron density theory (MEDT).10

Herein, as a continuation of our research program on 32CA reactions for the synthesis of novel polyfunctionalized spiroheterocycles,11 we report, for the first time, a facile and expeditious protocol for the synthesis of novel pyrene-grafted dispiro[indoline-3,2′-pyrrolidine-3′,3″-indolines] via the 32CA reaction of azomethine ylides (AYs) 3a−d (generated in situ from isatins 1a−d and sarcosine 2) to (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-ones 4a and 4b. This is followed by extensive theoretical investigations of all possible regio- and

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stereo-cycloaddition paths using global/local electrophilicity/nucleophilicity reactivity indices and the corresponding transition-state (TS) calculations at the (B3LYP/6-31G(d)) level of theory.

RESULTS AND DISCUSSION

Synthesis. The azomethine ylides (AYs) 3a–d were generated in situ from isatin derivatives 1a–d and sarcosine 2 and then trapped with (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-ones 4a and 4b as dipolarophiles, affording a series of hitherto unknown novel dispiro[indoline-3,2′-pyrrolidine-3′,3″-indolines] bearing pyrene moiety 5a–h (Scheme 1). The reactions were performed under three different conditions to examine the effect of solvent on the reaction time and yields. Different solvents such as toluene (nonpolar), acetonitrile (polar aprotic), and ethanol (polar protic) under reflux conditions were found to exert a substantial influence on the reaction yield. The results of this investigation are shown in Table 1.

As shown in Table 1, the pyrrolidine derivative 5 was obtained as a single regioisomer in good yields (65–96%) with relatively short reaction times (4–7.5 h) when the reactions were carried out in ethanol. Moderate yields (40–65%) were obtained and longer reaction time was observed when acetonitrile was used as a reaction solvent. On the other hand, poor yields (up to 26%) were obtained when the reactions were done in toluene as a reaction medium, even though the reaction time was extended to 16 h. A sensible interpretation of these findings may be attributed to the solvent polarity effect. Thus, as the polarity of the solvent is increased, the azomethine ylide (AY) is increasingly stabilized and consequently increases the percentage of reaction yield. A similar trend is consistently strong with protic solvent because of the strong influence of intermolecular hydrogen bonding. Besides, the electronic demand of the transition states is higher in polar and protic solvents than in nonpolar solvents. In polar protic solvents (e.g., ethanol), the transition state is more relatively stabilized than in aprotic (acetonitrile) and nonpolar (toluene) solvents.12

Regio- and Stereoselectivities. The 32CA reaction of nonstabilized azomethine ylides 3a–d, generated in situ via decarboxylation condensation of isatin derivatives 1a–d and sarcosine 2 to substituted (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-ones 4a and 4b proceeded in a highly regio- and diastereoselective manner, leading to the exclusive formation of one of four possible diastereomers in all cases. In a surprising twist, and unlike the regiochemical outcome observed previously11d with the β-addition of the same nonstabilized azomethine ylide to (E)-3-aryl-1-(pyren-1-yl)prop-2-en-1-ones as dipolarophiles (Figure 1a), the current

| product | R1 | R2 | R3 | time (h) | yield (%) | time (h) | yield (%) | time (h) | yield (%) |
|---------|----|----|----|---------|-----------|---------|-----------|---------|-----------|
| 5a      | H  | H  | H  | 16      | traces    | 9       | 65        | 4.5     | 96        |
| 5b      | H  | H  | CH3| 16      | 23        | 9       | 54        | 4       | 89        |
| 5c      | CH3| H  | H  | 16      | 26        | 9       | 48        | 4.5     | 69        |
| 5d      | H  | Cl | H  | 16      | 16        | 12      | 65        | 7       | 95        |
| 5e      | H  | Cl | CH3| 16      | 20        | 12      | 61        | 7       | 86        |
| 5f      | CH3| Cl | CH3| 16      | 23        | 12      | 40        | 7       | 65        |

“Reaction conditions: isatins 1a–d (1.2 mmol), sarcosine (2, 1.2 mmol), (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-ones 4a and 4b (1.0 mmol), solvent (10 mL)/reflux.
cycloaddition (CA) reaction to the (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-ones demonstrated opposite regioselectivity where the electron-rich carbon atom of the AY reacted with the \(\alpha\)-carbon of the enone (Figure 1b). Obviously, a combination of electronic (formation of a highly delocalized enolate anion; Figure 1a) and steric factors (preferential attack at secondary carbon as opposed to a hindered tertiary carbon; Figure 1b) working in concert dictates the preferential formation of one regioisomeric product.

Although one-step cycloaddition reactions are inherently diastereoselective and the relative stereochemistry of two stereogenic centers are predictable in the above reaction (C4′ and C3″/C3), one still expects the formation of two diastereomeric products due to the creation of a second spirocenter (C2′/C3) during the process (Scheme 1). Interestingly, the exclusive regioselective formation of only one isomer was obtained in all cases. Thus, to fully establish the chemical structures of the products and assign the relative stereochemistry of the stereocenters for the isolated diastereomer in each reaction, extensive one-dimensional (1D) \((1H-, 13C-, 13C-CRAPT NMR\)) and two-dimensional (2D) homonuclear and heteronuclear correlation NMR spectrometry experiments \((1H-1H-gDQFCOSY, 13C-1H-HSQCAD, 13C-1H-HMBCAD, 1H-1H-ROESYAD)\) as well as decoupling experiments were conducted in dimethyl sulfoxide (DMSO)-d6 on a selection of compounds (see the Supporting Information (SI)). Hence, using \(1,1′\)-dimethyl-4′-(1-pyrenoyl)-dispiro[indoline-3,2′-pyrrolidine-3,3″-indoline]-2,2″-dione (5c) as a representative example and a model for the remaining structurally related compounds, the relevant spectra that were used for regiochemical elucidation and stereochemical assignment are shown in Figure 2.

Regiochemical Assignment. Analysis of the \(13C\) (Figure 2, spectrum b, showing selected peak picking) and \(13C-CRAPT\) (see the Supporting Information) NMR spectra confirmed the presence of the expected 37 signals (17 aromatic CH’s, 11 aromatic quaternary carbons, 3 carbonyl carbons, 2 quaternary sp² spirocenters, 1 methane, 2 methyl, and 1 methine carbons), which is consistent with all carbons being non-equivalent. The three carbonyl carbons of the ketone and the indolinone rings resonate at \(\delta 200.5\) (C10), 177.3 (C2″, identified via long-range coupling with N1″−H), and 173.5 (C2) ppm, respectively. The two spirocyclic carbons of the pyrrolidine ring C2′/C3 (\(\delta\) 78.2 ppm) and C3′/C3″ (\(\delta\) 61.9 ppm) resonate furthest downfield relative to the remaining carbon atoms of this ring. While the methylene \(13C\) chemical shift (C4′/\(\delta\) 53.4 ppm) was clearly identified as the only signal with a negative phase in the \(1H-13C-HSQCAD\) spectrum (Figure 2, spectrum d), the attached diastereotopic protons appeared as two apparent triplets (\(\delta\) 4.64 (app t, \(J = 8.7\) Hz, 10.1 Hz).
1H, C5−Hb) and 3.56 (app t, J = 8.1 Hz, 1H, C5−Hc) ppm] and were correlated in the 1H−13C-HSQC-AD NMR spectrum by two contours to the corresponding C5 carbon (Figure 2, spectrum e). The methine proton signal (δ 5.28), which is the most deshielded aliphatic signal in the 1H NMR due to diamagnetic anisotropy, shows strong long-range 1H−13C heteronuclear multiple bond correlations (Figure 2, spectrum e) with the adjacent ketone (C10 δ 201 ppm, 2JCH), methylene carbon C5−H2 (33.4, 2JCH), spirocenter C5−/C1′ carbon (61.9 ppm, 2JCH), as well as the indoline carbonyl C2′- carbon (δ 177.2 ppm, 3JCH) and C9′- carbon (124.9 ppm, 3JCH) (Figure 2, spectrum f). The N1− methyl showed strong correlation contours with the C3′/C2′ spirocenter (3JCH) and C5−H2 (2JCH), thereby establishing a perfect match between the chemical shift values and the appropriate pyrrolidine ring atoms when used in conjunction with long-range 1H−13C coupling data observed from the methine proton signal. The 1H−13C heteronuclear multiple bond correlation data of N1−H of the indolinone ring were instrumental for identifying the chemical shifts of all carbon atoms associated with the indolinone five-membered ring (C2′, C3′, C5′, and C6′); meanwhile, the observed ROSEYAD correlation cross-peaks between N1−H and C7−H identified the chemical shift of the latter and triggered partial assignment of C4′−C7′ protons. Accordingly, from the 1H−1H-gCOSYAD correlation of C4′−H (off-diagonal cross-peak at δ 5.90/6.42) (Figure 2, spectrum c), the triplet at δ 6.42 was assigned to the adjacent proton C6′−H. The most diagnostic signal to distinguish the regioisomers was that of the methine group (C4−H) and its corresponding multiplicity. Thus, on first glance and based on observed semilinal and vicinal correlations between C4−H, C5−Hα, and C5−H in the gDQFCOSY (Figure 2, spectrum c), one immediately infers that the methine and the methylene groups are spin-coupled, clearly supporting the proposed structure 5 (Scheme 1) and ruling against the nonobserved regioisomer 6, in which the same groups are isolated.

**Stereocchemical Assignment.** Although the C4−H multiplicity was expected to be doublet of doublets (dd) due to the neighboring nonequivalent diastereotopic protons, it appeared as a highly shifted downfield apparent triplet at δ 5.28 ppm (app t, J = 8.3 Hz, 1H, C4−H) and was correlated to the carbon at δ 53.2 ppm. The three nonequivalent pyrrolidine protons were totally correlated with the same-spin system by 1H−1H-gDQFCOSY (nine-contour square in the aliphatic region (Figure 2, spectrum c)), and the corresponding 13C chemical shifts were also confirmed based on 1H−13C-gHSQC-AD cross-peaks (Figure 2, spectrum d). Clearly, the magnetic anisotropic effect impacted the chemical shifts for the pyrrolidine carbons and more so for its protons and outweighed the local atomic environment effect, which warranted the above detailed NMR investigations. Pleasantly, the N1−CH3 (δ 2.77 ppm/1H NMR) group of the indolino moiety (Figure 2, spectrum a) provided the only entry point that ultimately led to the unambiguous assignment of the correct stereochemistry for the isolated diastereomer. In the ROSEYAD NMR spectrum (Figure 2, spectrum f), there exists a strong correlation cross-peak between the N1−CH3 protons (δ 2.77 ppm) and H-7 (d, δ 6.75 ppm), and identification of the latter triggers the partial assignment of all of the indoline ring protons C4−H−C7−H. Therefore, from the 1H−1H-gCOSYAD correlation of C7−H (off-diagonal cross-peak at δ 6.75/7.25) (Figure 2, spectrum c), the overlapped triplet at δ 7.25 was assigned to the adjacent proton C6′−H. Thus, it appears that the two overlapped signals in the range δ 7.27−7.25 ppm arise from two different indoline aromatic rings (vide infra). Thus, from the correlation of the δ 7.25 signal, as evident from the contour at δ 7.27/6.36, the triplet at δ 6.36 was tentatively assigned to C6−H and suggested that the overlapped signals in the range δ 7.27−7.25 comprise a
doublet (C₄′−H) and a triplet (C₅−H). However, this warranted further investigation, which could only be resolved through $^1$H−$^1$H homonuclear decoupling experiments (vide infra).

It is noted, though, because of the overlap between two signals at $\delta$ 7.27−7.25 ppm, $^1$H−$^1$H-gDQFCOSY cross-peaks were insufficient to totally correlate the C₄′−H−C₅−H spin system and make a clear distinction between signals belonging to the latter and those stemming from the other indolinone C₄′−H−C₅−H spin system. Thus, homonuclear decoupling experiments (Figure 3) were conducted to match the chemical shifts of indolinone protons with their respective positions on the indolinone aromatic ring. Hence, irradiation of C₅−Hₐ (Figure 3, spectrum b), C₄′−H (Figure 3, spectrum c), C₅′−H (Figure 3, spectrum d), C₅″−H (Figure 3, spectrum e), C₆−H (Figure 3, spectrum f), C₅′−H (Figure 3, spectrum g), C₆−H (Figure 3, spectrum h), C₅−H (Figure 3, spectrum i), and C₆′−H (Figure 3, spectrum j) resulted in the collapse of C₄′−H/C₅−H into doublets, C₅′−H/C₆−H into doublets, C₆−H into a doublet, C₄′−H into a singlet, C₅−H into a singlet, C₆−H into a doublet, C₅−H into a singlet, and C₆′−H into a doublet. These studies led to the unambiguous assignment of the chemical shifts for the indolinone protons, and setting the relative stereochemistry for the C₃′/C₂′ spirocenter and C₄′−H. Further evidence to support the syn relationship between C₄′−Hₐ and C₅−H, which was key for stereochemical assignment, was clear in derivative 5h, while the C₅−Hₐ and C₄′−H trans coupling constant was much smaller (C₅−Hₐ/C₄′−H, $^\text{J}$ = 11.1 Hz), while the C₅−Hₐ and C₄′−H trans coupling constant was much smaller (C₅−Hₐ/C₄′−H, $^\text{J}$ = 6.8 Hz) (Figure 4).

The syn geometry of the C₄′−H and C₃′/C₅′ carbonyl was evident from the absence of relevant off-diagonal cross-peaks with the aromatic protons C₄′−H−C₅−H. In addition, the syn geometry was expected since it would be retained as a result of the inherently diastereoselective one-step 32CA reaction of an (E)-azomethine ylide [(E)-AY].

**32CA Reaction Mechanism.** As suggested in Scheme 2, the regio- and stereochemistries for the formation of pyrrolidine derivatives 5a−h rather than the corresponding adducts 6a−h are described by considering the steric factor and the repulsion force. The formation of pyrrolidine derivatives 5a−h proceeds through path A where the nucleophilic carbon of the AY attacked the less hindered carbon of the ethylene derivatives 4a and 4b (α-attack) via “exo”-transition state. This can be explicated by the fact that the corresponding “endo”-transition state would require extra free energy of activation than the exo-transition state due to the electrostatic repulsion between the cis carbonyl groups increasing the free energy of activation. On the other hand, concerning path B where the electron-rich carbon atom of the AY attacked the more hindered site of the ethylene derivative 4a, more free energy of activation would be exerted due to the steric effect of the 3° carbon, which could exclude such a path of attack. In addition, the mechanism is illustrated using orbitals (Figures S42).

**Computational Studies.** Energies of Transition-State Structures. As experimentally substantiated, only the isomer of 5a−h could be isolated and 6a−h was not observed at all. It was postulated that regioselectivity curbs the formation of 6a−h (Scheme 2), whereas stereoselectivity restricts the formation of the 5-endo adduct isomer. Therefore, a computational study has been carried out to elucidate the energetics of the reaction.
Scheme 2. Plausible Mechanism for the Formation of Dispiro[indoline-3,2′-pyrrolidine-3′,3″-indolines] 5a–h

paths A and B via exo- and endo-TS for the formation of 5a and 6a, starting from 3a and 4a. Figure 5 represents the computed free-energy profile of the most stable molecular complexes, transition states (exo-TS and endo-TS), unstable intermediates, and the products of reaction paths A and B.

It is obvious from the formation energies (Figure 5) that the nonbonded molecular complex in exo orientation in path A (α attack) is energetically the most favorable orientation, thus confirming the regioselectivity of the reaction. Stereoselectivity can be explained from the activation energies for the formation of 5a and 6a via exo- and endo-TS. The activation energy for the formation of 5a-exo is the lowest among the other stereoisomer 5a-endo as well as 6a-exo/endo (Figure 5). Although energetically, the 5a-endo isomer was found to be more stable than 5a-exo, due to the higher activation energy barrier, it was not formed. Further, as the energy of exo-TS in path A is less than that of the reactants combined (3a + 4a), the formation of 5a-exo appears to be barrierless; however, it is not barrierless for compound 5a-endo or 6a-exo/endo (Figure 5). The effect of substituents on the transition-state stability has been estimated (Figure S41). It is notable that the TS energies varied within 2 kcal/mol for 5b (R₁ = C₉H₃), 5c (R₃ = CH₃), and 5e (R² = Cl) as examples. Generally, no significant effects of substituents on the TS have been observed.

The optimized geometries of exo- and endo-TS in paths A and B are given in Figures 6 and 7, respectively. The potential energy surface (PES), as depicted in Figure 8, suggests that the reaction takes place through a one-step two-stage mechanism (Figure 9); first, the 5′···4′ bond is formed and then the 2′···3′ bond is formed.

It should be noted at this point that the molecular mechanism of these types of reactions is not well understood. Frequently, the literature is plagued by a confidence in a one-step two-stage mechanism of 32CA,14 and this is regardless of the structure of the cycloaddends (reactants). It is worth mentioning that a body of scientific work challenging this view has been published recently.15 Interestingly, a broad range of mechanisms are now known to occur, proceeding through
Figure 5. Computed free-energy profile of the optimized lowest-energy conformers. In path A, the solid lines connect the intermediates and transition states of the 5a-exo (3S,3′R,4′S) formation path, and the dotted lines connect the intermediates and TS of the 5a-endo (3R,3′R,4′S) formation path. In path B, the solid lines connect the intermediates and transition states of the 6a-exo (3S,3′S,4′R) formation path, and the dotted lines connect the intermediates and TS of the 6a-endo (3R,3′S,4′R) formation path. Relative free energies are given in kcal/mol.

Figure 6. Optimized geometries and global electron density transfer (GEDT) at exo-TS (a) and endo-TS (b) in path A. The 5′···4′ and 2′···3′ bond distances are shown with cyan arrows. The green arrow indicates the direction of GEDT.

Figure 7. Optimized geometries GEDT at exo-TS (a) and endo-TS (b) in path B. The 5′···4′ and 2′···3′ bond distances are shown with cyan arrows. The green arrow indicates the direction of GEDT.

Figure 8. Potential energy surfaces (PESs) of path A via exo-TS (a) and endo-TS (b) formation reaction as obtained by perturbation of the 5′···4′ (SC2) and 2′···3′ (SC1) bonds. The total electronic energies in the z-axis are given in hartree/particle.
transition states (TSs) with a range of synchronicities and polarities. Consequently, we can suggest that these processes proceed by a one-step mechanism through asynchronous transition states. According to the latest terminology, they should be considered polar but not definitely stepwise processes.

Analysis of the Global/Local Electrophilicity/Nucleophilicity Reactivity Indices. The conceptual density functional theory (CDFT) in the last four decades affords various indices to rationalize and understand the chemical structures. The concepts that materialize from this theory have also been extensively used to generate a broad approach to the description of chemical reactivity. Accordingly, structures of azomethine ylides \(3\alpha-\)d and ethylene derivatives \(4a\) and \(4b\) in this work were minimized according to the parameters described.

Additionally, theoretical quantitative scales have been shown to be powerful means rationalizing the reactivity of a wide variety of chemical species. These scales have become an appropriate and useful tool as they can be used to justify the electronic aspects of reactivity, selectivity, and their variations induced by field effects due to conformational changes or arising from chemical substitution.

Many global and local reactivity descriptors, defined within the density functional theory (DFT), have been anticipated and shown to be very beneficial in the study and interpretation of reactivity and regioselectivity in polar reactions. Well known among these reactivity indices, chemical potential \(\mu\), chemical hardness \(\eta\), and global electrophilicity \(\omega\), can be cited.

In this context, the electrophilicity index \(\omega\) has shown to be a powerful theoretical means to predict the electrophilic behavior. Indeed, \(\omega\) measures the stabilization in energy when a molecule acquires from the environment a supplementary electronic charge. For this reason, the electrophilicity index takes into account both the propensity of the molecule to acquire an additional electronic charge and the resistance of the system to exchange charge with the environment. The calculated values of \(\mu\) and \(\eta\) as well as the electrophilicity index \(\omega\), are presented in Table 2.

The data summarized in Table 2 reveal that the electronic chemical potentials, \(\mu\), of azomethine ylides (AYs) \(3\alpha-\)d \((-3.36 < \mu < -2.96 \text{ eV})\) are higher than that of ethylene derivatives \(4a\) and \(4b\), \(\mu \approx -4.13\) and \(-4.10 \text{ eV}\).

Additionally, the azomethine ylides \(3\alpha-d\) with configuration “E” have an electronic chemical potential higher than its dipole counterparts azomethine ylides \(3\alpha-d\) with configuration “Z”, which means that the electronic flow is again from the \(E\)-configuration azomethine ylides \(3\alpha-d\) to \((E)-3-((2\text{-exo-2(-pyren-1-yl)}\text{ethylidene})\text{indol}-2\text{-ones})\) \(4a\) and \(4b\) as dipolarophile. Therefore, the ethylene derivatives \(4a\) and \(4b\) act as electrophiles due to the larger value of their \(\omega\) \((2.97 < \omega < 3.03)\) relative to the \(\omega\) \((1.30 < \omega < 1.76)\) values of AYs \(3\alpha-\)d.

It is important to mention that a recent study on the electrophilicity index of reagents involved in CA reactions permitted to develop a unique electrophilicity scale. In a study of a set of organic molecules, this scale allowed us to classify these molecules as strong, \(\omega > 1.5 \text{ eV}\), moderate, \(0.8 < \omega < 1.5 \text{ eV}\), and marginal electrophiles \(\omega < 0.8 \text{ eV}\). Interestingly, this allows us to place our ethylene derivatives \(4a\) and \(4b\) with strong molecules in this scale of electrophilicity, as well as azomethine ylides \(3c\) and \(d\) but less than \(4a\) and \(4b\), while the azomethine ylides \(3a\) and \(3b\) located at the bottom of the electrophilicity scale, which are classified as marginal electrophiles, correspond to good nucleophiles. Moreover, a more systematic study in the same line has used the \(\omega\) values to classify azomethine ylides and ethylene derivatives on a unique scale. On the other hand, the global electron density transfer (GEDT) calculations at TSs have been performed. The GEDT value of \(0.24e\) at \(5a\)-exo-TS indicates the polar nature of the reaction (Figures 6 and 7).

Recently, Domingo et al. showed during the study on captodative (CD) ethylenes (Scheme 3), in which the molecule bears more than one functional group with opposite electronic demand, that this type of molecules can behave as good electrophiles and good nucleophiles. Therefore,
suitable information about the nucleophilicity pattern of reactivity would be desirable. In this sense, the simplest approach to have a different descriptor to give further information about the nucleophilicity has been proposed. Based on this idea, an empirical (relative) nucleophilicity index \( N \) has been introduced, relating the nucleophilicity with the highest occupied molecular orbital (HOMO) energy obtained within the Kohn–Sham scheme. A subsequent study involving a wide series of substituted alkenes compounds, as well as substituted aromatic compounds and simple nucleophilic molecules, supported the usefulness of the nucleophilicity \( N \) index in the nucleophilicity model. In this latter study, such a model permitted to classify organic molecules as strong, \( N > 3.00 \text{ eV} \), moderate, \( 2.00 \text{ eV} < N < 3.00 \text{ eV} \), and marginal nucleophiles, \( N < 2.00 \text{ eV} \).

Therefore, by examining the nucleophilicity descriptor \( N \) for these compounds calculated and given in Table 2, we found that the azomethine ylides and ethylene derivatives being classified as a strong nucleophile and azomethine ylide \( 3b \) (\( N = 6.87 \text{ eV} \)) represents the best nucleophile of this series. These results are reliable with the expected reactivity pattern (Table 2).

To understand the observed regioselectivity in the cycloaddition reactions, apart from global properties, local parameters of reactivity, including the condensed-to-atom electrophilic and nucleophilic Parr and PY Fukui functions and the local electrophilicity index defined by \( \omega_k = \omega P_k \), are necessary to differentiate the reactive behavior of atoms forming a molecule.

Several studies have established that the main difference between the regioisomer reaction pathways is essentially related to the orientation of the two asymmetric fragments (dipole and dipolarophile), in which the most favorable regioisomeric reactive channel is that implying the most favorable local electrophilic and nucleophilic interactions. Consider, for instance, the interaction between azomethine ylides \( 3a \) and \( 3c \), and ethylene derivative \( 4a \), which, according to our classification, will show a global electrophilicity difference \( \Delta \omega = 1.67 \) and \( 1.44 \), respectively. Therefore, an analysis of the local reactivity index in these selected three neutral organic molecules, participating in polar CA reactions, was performed (see the Supporting Information).

From Table 3, it may be seen on the basis of the local descriptor that the highest values of \( P_k^e \) in azomethine ylides \( 3a \) and \( 3c \) located at the carbon atom C9 are 0.39 and 0.36, respectively. Furthermore, for the ethylene derivative \( 4a \), C2 carbon represents the electrophilic site with a local electrophilicity value of \( \omega_k = 0.34 \text{ eV} \). Therefore, the interaction will take place between the C9 center of azomethine ylides \( 3a-d \) and the C2 center of ethylene derivatives \( 4a \) and \( 4b \). This result is consistent with the experimental observation, establishing the fact that the CA process between azomethine ylides \( 3a-d \) and ethylene derivatives \( 4a \) and \( 4b \) occurs through interaction between \( C_9^N-C_{\text{ethyl}} \) and then \( C_9^N-C_2^e \), leading to the formation of the pyrrolidine derivatives \( 5a-h \) (Scheme 2, Figures 5 and 9).

It is concluded that the computed electrophilic/nucleophilic Parr functions and Parr–Yang Fukui functions of the reagents involved in CA reactions can explain not only the regioselectivity and chemoselectivity but also the reactivity based on two-center electrophilic–nucleophilic interactions.

**CONCLUSIONS**

In conclusion, an efficient protocol has been developed for the facile synthesis of functionalized dispiro[indoline-3,2′-pyrrolidine-3,3′-indolines] via a one-pot three-component 32CA of

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**Table 3. Electrophilic and Nucleophilic Parr and PY Fukui Functions for the Most Relevant Heavy Atoms of Azomethine Ylides 3a and 3c and Ethylene Derivative 4a**

| Site k | \( P_k^e \) | \( P_k^a \) | \( f_k^e \) | \( f_k^a \) |
|--------|--------------|--------------|--------------|--------------|
| 3a C   | -0.06        | 0.34         | 0.05         | 0.24         |
| 3a C   | 0.75         | 0.39         | 0.47         | 0.23         |
| 3a N   | 0.21         | -0.13        | 0.22         | 0.008        |
| 3a C   | -0.06        | 0.33         | 0.05         | 0.23         |
| 3a C   | 0.75         | 0.36         | 0.47         | 0.22         |
| 3a N   | 0.20         | -0.12        | 0.22         | 0.007        |
| 4a C   | 0.14         | -0.01        | 0.15         | 0.005        |
| 4a C   | 0.11         | 0.04         | 0.14         | 0.004        |
| 4a C   | 0.10         | -0.02        | 0.12         | 0.005        |
| 4a O   | 0.21         | 0.00         | 0.13         | 0.02         |

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the azomethine ylides with (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-one derivatives. The pure products were obtained by recrystallization without requiring further purification techniques. The chemical structures of the obtained regioselective products were confirmed on the basis of both 1D and 2D NMR spectroscopy. DFT calculations showed that the formation energies indicate that 32CAs proceed via a one-step two-stage mechanism through asynchronous transition states and the favored reaction path leads to α-adduct path, the most favorable orientation, which well agrees with experimental observations and confirms the regioselectivity of the reaction. The electrophilic/nucleophilic character of a series of azomethine ylides 3a–d and ethylene derivatives 4a and 4b involved in polar CA reactions has been studied. The global electrophilicity pattern of the azomethine ylides and ethylene derivatives involved in the reactions have been quantitatively established in terms of the electrophilicity index ω. The global nucleophilicity values (N) of molecules used in this work have been calculated. Analysis of the reactivity indices based on the frontier molecular orbitals explains the reactivity of these species in polar CA reactions and has been found to correlate well with the experimental results. It is worth mentioning that the obtained data based on experimental, spectral, and theoretical calculations will open a new window in the field of CA reactions.

## EXPERIMENTAL SECTION

All solvents purchased from Sigma-Aldrich are of spectroscopic grade and used without further purifications. Melting points were determined on a Stuart S80 melting point apparatus and are uncorrected. NMR spectra were acquired on a Varian NMR instrument (at 400 MHz for 1H, 100 MHz for 13C) and a Bruker Avance III HD NMR spectrometer (600 MHz for 1H, 150 MHz for 13C) in DMSO-d6 solutions, using residual solvent signals as internal standards. Elemental analyses were performed on a Vario EL v2.3 elemental analyzer; the results were found to be in good agreement with the calculated values (±0.3%). The dipolarophiles (E)-3-(2-oxo-2-(pyren-1-yl)ethylidene)indolin-2-ones 4a and 4b were prepared according to the literature procedure. 3a

### Computational Details

Geometry optimizations were performed on 3a, 4a, 5a, and 6a in vacuo with density functional theory (DFT) using B3LYP exchange correlation functional and People’s double ξ basis set (6-31G) with added polarization function on the heavy atoms (B3LYP/6-31G(d)). Frequency calculations were performed on the optimized geometries using the same level of theory. The formation of S→ 4′ and 2′ → 3′ bonds in both 5a and 6a was probed by bond length perturbation followed by geometry optimization at each point, generating a potential energy surface (PES). Transition-state structures were optimized using the TS guess geometry obtained from PES with the QST3 method, as implemented in Gaussian 16. The nature of the TS was confirmed by computing the frequency modes on the optimized TS geometries using the same level of theory. Further, intrinsic reaction coordinate (IRC) scans were performed in both directions starting from each TS (see the Supporting Information). Coordinates for the optimized geometries are given in the Supporting Information (SI). Relative energies were calculated with respect to the sum of the energies of the separated reactants. The energy values were converted to kilocalories per mole from hartree/particle using the conversion factor of 627.509467.

The global electronic properties of azomethine ylides 3a–d and ethylene derivatives 4a and 4b were estimated according to the equations recommended earlier by Parr and Domingo. Both quantities of electronic chemical potential (μ) and chemical hardness (η) are obtained from one-electron energies of the frontier molecular orbital HOMO and lowest unoccupied molecular orbital (LUMO), εH and εL (Table S1), as μ = (εH + εL)/2 and η = (εL − εH), respectively. Next, global electrophilicity (ω) is given using electronic chemical potential (μ) and chemical hardness (η) according to the formula

ω = μ2/2η

Subsequently, global nucleophilicity (N) can be expressed by the following equation

N = E_HOMO (eV) − E_HOMO(TCE) (eV)

where tetracyanoethylene (TCE) was taken as reference because it presents the lowest HOMO energy in a long series of organic molecules already investigated in polar CA contexts.

Regional Fukui functions for electrophilic (fk) and nucleophilic (fl) attacks were obtained from a single-point calculation at the optimized structures of the GS of molecules by a method described elsewhere.

The electrophilic (P(k)) and nucleophilic (P(l)) Fukui functions were obtained through the analysis of the Mulliken AOS of the radical anion and the radical cation by single-point energy calculations over the optimized neutral geometries using the unrestricted UB3LYP formalism for radical species. 33

**Synthetic Procedure.** General Procedure for the Synthesis of Dispiro[indoline-3,2′-pyrrolidine-3′,3″-indoline]-2,2″-dione 5a–h. A mixture of isatin 1 (1.2 mmol), sarcosine 2 (107 mg, 1.2 mmol), and chalcone 4 (1 mmol) in absolute ethanol (10 mL) was stirred at reflux for 4–7.5 h and then cooled to room temperature. The solid formed in the reaction mixture was filtered off, washed with n-hexane, and recrystallized from ethanol to obtain the pure cycloadduct 5a–h.

**35,3′R,4′S′-1′-Methyl-4′-(1-pyrenyl)-dispiro[indoline-3,2′-pyrrolidine-3′,3″-indoline]-2,2″-dione (5a).** Yield 525 mg (96%) from 176 mg of 1a and 375 mg of 4a; pale yellow crystals, mp 239–240 °C. 1H NMR (DMSO-d6, 600 MHz) δ 10.05 (s, 1H, N1−H), 9.92 (s, 1H, N1−H), 8.31–8.20 (m, 4Hpyrene), 8.13–8.08 (m, 5Hpyrene), 7.53 (dd, J = 6.6, 1H, C5−H), 7.32 (dd, J = 6.6 Hz, 1H, C4−H), 7.12 (t, J = 6.6 Hz, 1H, C6−H), 6.95 (t, J = 6.6 Hz, 1H, C6−H), 6.54 (d, J = 6.6 Hz, 1H, C4−H), 6.41 (td, J = 7.2, 1.8 Hz, 1H, C7−H), 6.36 (d, J = 7.2 Hz, 1H, C7−H), 5.90 (d, J = 7.2 Hz, 1H, C7−H), 5.23 (app, J = 7.2 Hz, 1H, C4−H), 4.59 (app, J = 8.4 Hz, 1H, C5−H), 3.52 (app, J = 8.4 Hz, 1H, C5−H). 13C NMR (DMSO-d6, 150 MHz) δ 201.1 (q, C9o), 177.9 (q, C9′), 175.6 (q, C9′), 143.1 (q, C9o), 141.9 (q, C9o), 133.2 (q, C9′), 132.5 (q, C9′), 130.9 (q, C9′), 130.3 (CHpyrene), 129.8 (q, C9o), 129.7 (CHpyrene), 128.9 (CHpyrene), 128.8 (q, C9′), 128.5 (CHpyrene), 128.2 (CHpyrene), 127.5 (CHpyrene), 127.4 (CHpyrene), 127.0 (CHpyrene), 126.7 (CHpyrene), 126.4 (2 × CHpyrene), 125.6 (q, C9o), 125.4 (q, C9′), 125.1 (CHpyrene), 124.1 (q, C9′), 124.0 (CHpyrene), 123.6 (q, C9′), 121.7 (C10H), 120.7 (C10H), 109.5 (C10H), 108.5 (C10H), 78.7 (C10H), 62.2 (C10H), 53.8 (C10H), 53.7 (C10H), 35.3 (N1−CH3) ppm. Anal. Calcd for C30H21N2O3: C, 78.96; H, 4.60; N, 7.67. Found: C, 78.75; H, 4.39; N, 7.49.
Yield 511 mg (91%) from 176 mg of 1a and 387 mg of 4b; yellow crystals, mp 227–228 °C. 1H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 10.09 (s, 1H, $\text{N}-\text{H}$), 8.43–8.31 (m, 4H$_{\text{pyrene}}$), 8.28 (d, $J = 9.1$ Hz, 1H$_{\text{pyrene}}$), 8.23 (d, $J = 8.1$ Hz, 1H$_{\text{pyrene}}$), 8.19–8.05 (m, 3H$_{\text{pyrene}}$), 7.39 (dd, $J = 7.5, 0.9$ Hz, 1H, $\text{C}_{5\text{H}}$), 7.16 (d, $J = 8.0$ Hz, 1H, $\text{C}_{5\text{H}}$), 7.03 (t, $J = 7.9$ Hz, 1H, $\text{C}_{5\text{H}}$), 6.85 (d, $J = 8.0$ Hz, 1H, $\text{C}_{5\text{H}}$), 6.54 (t, $J = 8.4$ Hz, 1H, $\text{C}_{5\text{H}}$), 6.45 (td, $J = 7.6, 1.8$ Hz, 1H, $\text{C}_{5\text{H}}$), 6.35 (d, $J = 8.2$ Hz, 1H, $\text{C}_{5\text{H}}$), 5.94 (d, $J = 8.0$ Hz, 1H, $\text{C}_{5\text{H}}$), 5.27 (app t, $J = 8.3$ Hz, 1H, $\text{C}_{5\text{H}}$), 4.58 (app t, $J = 8.7$ Hz, 1H, $\text{C}_{5\text{H}}$), 3.84 (app t, $J = 8.1$ Hz, 1H, $\text{C}_{5\text{H}}$), 2.40 (s, 3H, $\text{N}-\text{CH}_3$), 1.95 (s, 3H, $\text{N}-\text{CH}_3$), 2.04 (s, $\text{N}-\text{CH}_3$). Anal. Calcd for C$_{37}$H$_{27}$N$_3$O$_3$: C, 79.13; H, 4.85; N, 7.48.
NMR spectra of the synthesized compounds; potential energy surfaces (PES) of path B; intrinsic reaction coordinates (IRCs) connecting the reactant and the products via exo/endo-TS; potential energy diagram for the 2′−3′ bond length perturbation in 6a-exo and 6a-endo; coordinates of the optimized geometries; frontier orbital energies (eV) for A′s 3a−d and ethylene derivatives 4a and 4b; effect of substitutions on the energetics of the cycloaddition reaction; Parr function of 3a−c, 4a, and 4b; and condensed-to-atom Fukui functions of 3a, 3c, and 4a (PDF)

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**Notes**

The authors declare no competing financial interest.

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