Brønsted Acid Catalyzed (4 + 2) Cyclocondensation of 3-Substituted Indoles with Donor−Acceptor Cyclopropanes

Alesandere Ortega, Uxue Uria,* Tomás Tejero, Liher Prieto, Efraim Reyes, Pedro Merino,* and Jose L. Vicario*

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ABSTRACT: Acylcyclopropanes are employed as useful donor−acceptor cyclopropanes that undergo formal (4 + 2) cyclocondensation with N-unprotected 3-substituted indoles in the presence of a Brønsted acid catalyst. The reaction involves the simultaneous alkylation of both the N and C-2 positions of the indole and provides access to the 8,9-dihydropyrido[1,2-a]indole scaffold that is the central core of several biologically relevant indole alkaloids in excellent yields and good selectivities.

Donor−acceptor cyclopropanes (DAC) have demonstrated to be very useful functionalized reagents in modern organic synthesis. These compounds have an enhanced tendency to undergo ring opening in the presence of an external reagent and/or a catalyst to release ring strain, which is also facilitated by the synergistic nature of the electron-withdrawing and electron-donating substituents that contributes to the stabilization of the zwitterionic species formed after the ring-opening event. Despite this chemistry being well-known for decades, the use of these particular strained reagents as suitable substrates for the construction of carbocyclic and heterocyclic scaffolds through formal cycloaddition chemistry has experienced a renaissance in the past few years. In particular, the chemical behavior of indoles when reacted with donor−acceptor cyclopropanes has been studied in detail by several research groups, showing that different products can be obtained depending on the reaction conditions or on the substitution pattern of the nucleophilic indole reagent (Scheme 1). In general, donor−acceptor cyclopropanes react with indoles providing the corresponding C2 or C3 alkylation products depending on whether substituents at these positions are already present or not at the starting indole reagent (Scheme 1a), or alternatively, they undergo dearomative (3 + 2) cycloaddition reaction leading to hexahydrocyclopenta[b]-indoles (Scheme 1b). In all cases, the initial ring opening has been reported to be possible through either Lewis acids or strong Bronsted acids as promoters.

We wish to report herein the interesting alternative behavior observed when a donor−acceptor cyclopropane incorporating an acyl moiety as the electron-withdrawing group reacts with N-unprotected C3-substituted indoles under Bronsted acid catalysis (Scheme 1c). In this case, indole acts as a double nucleophile that, after C-2 alkylation, undergoes intramolecular condensation with the ketone moiety providing a (4 + 2) cyclocondensation product with a general 8,9-dihydropyrido[1,2-a]indole architecture present in the core structure of many natural occurring indole alkaloids with relevant biological activity. While there are many methods to access this scaffold, the approach shown herein is unconventional and provides multiple possibilities for the introduction of variable substitution patterns. There is only one previous example of a (4 + 2) cyclocondensation between indoles and donor−acceptor cyclopropanes, but in this case the reaction

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involves the subsequent C2 and C3 alkylation to form a carbazole derivative as the final adduct.\textsuperscript{9}

We initially optimized the experimental conditions for the reaction to proceed in the most efficient way, using cyclopropane \(1a\)\textsuperscript{10} and 3-methyl-1H-indole (2a) as model substrates (Table 1). We first evaluated the performance of diphenylphosphoric acid as catalyst, observing the formation of the expected cyclocondensation adduct 3a\textsuperscript{11} together with minor amounts of regioisomeric product 4a (entry 1). This compound arises from the competitive participation of the indole as an N-nucleophile reacting with the carbocation formed after the acid-catalyzed ring opening. Other acid catalysts were next surveyed, observing that less acidic acetic acid was unable to promote the reaction (entry 2) but more acidic Brønsted acids led to the formation of products 3a and 4a in varying ratios with similar levels of chemical efficiency (entries 3–8). From all acids tested, N-trifluoromethanesulfonyl diphenylphosphoramidate was found to provide the best results in terms of overall yield and regioselectivity (entry 6). Solvents of varying nature were tested with this catalyst, and it was observed that moving to a more polar solvent like THF suppressed the reaction (entry 9) while changing to chloroform (entry 10) or other arenes (entries 11–12) did not result in any significant improvement in the outcome of the reaction. Finally, the effect of the temperature was also evaluated (entries 13–14). Lower temperatures were observed to suppress the reaction, while at higher temperatures the reaction proceeded with better yield and regioselectivity, obtaining the best results when the reaction was carried out at 100 °C (entry 14).

With an optimized protocol in hand, we next evaluated the applicability of this new transformation and the possibilities offered by the two reaction partners to incorporate structural diversity. We started by surveying the performance of indoles with a variable substitution pattern both at the 3-position or at other positions within the aryl moiety in combination with cyclopropane 1a (Table 2). As it can be seen in this table, a collection of 3-methylindole reagents with both electron-donating or electron-withdrawing substituents at the 5-, 6-, or 7-position provided the corresponding cyclocondensation products 3a–f in good yields and with high selectivity (entries 1–6), only detecting the competitive formation of regioisomers 4a–f in minor amounts in all cases. In addition, the reaction also demonstrated a wide scope with respect to the substituent placed at the 3-position of the indole reagent (entries 7–9), although the yield was significantly affected by

| Table 1. Optimization of the Reaction\textsuperscript{a} |
|---|
| entry | catalyst | solvent | T (°C) | time (h) | yield (%) | 3a/4a (%) |
| 1 | (PhO)₂P(O)OH | Toluene | 50 | 72 | 50 | 1.8/1 |
| 2 | AcOH | Toluene | 50 | 72 | <5 | n.d. \textsuperscript{d} |
| 3 | (+)-CSA | Toluene | 50 | 12 | 69 | 1/1 |
| 4 | CF₃CO₂H | Toluene | 50 | 24 | 39 | 2.5/1 |
| 5 | p-TsOH | Toluene | 50 | 12 | 59 | 1.3/1 |
| 6 | (PhO)₂P(O)NHTf | Toluene | 50 | 12 | 61 | 2.5/1 |
| 7 | NHTf₂ | Toluene | 50 | 12 | 51 | 3.8/1 |
| 8 | Conc. HCl (aq.) | Toluene | 50 | 12 | 66 | 1.2/1 |
| 9 | (PhO)₂P(O)NHTf | THF | 50 | 12 | <5 | n.d. \textsuperscript{d} |
| 10 | (PhO)₂P(O)NHTf | CHCl₃ | 50 | 12 | 63 | 2/1 |
| 11 | (PhO)₂P(O)NHTf | C₆H₆ | 50 | 12 | 61 | 2.5/1 |
| 12 | (PhO)₂P(O)NHTf | m-Xylene | 50 | 12 | 59 | 2.5/1 |
| 13 | (PhO)₂P(O)NHTf | Toluene | r.t. | 96 | <5 | n.d. \textsuperscript{d} |
| 14 | (PhO)₂P(O)NHTf | Toluene | 100 | 2 | 60 | 5/1 |

\textsuperscript{a}Reactions carried out with 0.05 mmol of 1a and 2a, using 10 mol % of catalyst in 0.25 mL of solvent until consumption of starting material. \textsuperscript{b}Combined yield of both regioisomers. \textsuperscript{c}Calculated by NMR analysis of crude reaction mixture. \textsuperscript{d}n.d. = not determined.

| Table 2. Scope of the Reaction: Indole Reagent\textsuperscript{a} |
|---|
| entry | indole (2) \textsuperscript{f} | R\textsuperscript{1} | R\textsuperscript{2} | yield (%) \textsuperscript{b} | 3/4 (%) \textsuperscript{c} |
| 1 | 2a | Me | H | 59 (50) | 5:1 |
| 2 | 2b | Me | 7-Me | 58 (54) | 13:1 |
| 3 | 2c | Me | 6-OMe | 61 (61) | >20:1 |
| 4 | 2d | Me | 6-Me | 60 (52) | 6:1 |
| 5 | 2e | Me | 6-F | 65 (60) | 10:1 |
| 6 | 2f | Me | 5-OMe | 50 (42) | 5:1 |
| 7 | 2g | Et | H | 56 (46) | 4:3:1 |
| 8 | 2h | Pr | H | 25 (25) | >20:1 |
| 9 | 2i | tBu | H | 14 (14) | >20:1 |
| 10 | 2j | Bn | H | 60 (47) | 3:4:1 |
| 11 | 2k | CH₂CH=CH₂ | H | 57 (36) | 1:5:1 |
| 12 | 2l | Ph | H | 69 (62) | 7:6:1 |
| 13 | 2m | 4-FC₆H₄ | H | 82 (73) | 8:1 |
| 14 | 2n | 4-MeOC₆H₄ | H | 85 (79) | 11:1 |

\textsuperscript{a}All reactions were carried out at 0.05 mmol scale of 1a and 2a–n, with 10 mol % of cat. in 0.25 mL of toluene until consumption of starting material. \textsuperscript{b}Combined yield of both regioisomers. \textsuperscript{c}Calculated by NMR analysis of crude reaction mixture.
the steric bulk of this substituent. Finally, indoles with functionalized side chains such as benzyl or allyl (entries 10 and 11) and 3-aryl indoles also exhibited high reactivity, providing the desired cyclocondensation products in very high yields and regioselectivities (entries 12−14).

We next evaluated other cyclopropane substrates (Table 3), starting with cyclopropyl ketones 1b−d. These reacted with a variety of 3-substituted indoles. In all cases, the exclusive formation of adducts 5a−e occurred without any N-addition byproduct (entries 1−5). We next surveyed cyclopropane 1e that incorporates two electron-withdrawing substituents as a potentially more reactive substrate. Indeed, the reaction with 2a led to the exclusive formation of product 5f in excellent yield (entry 6) and also without the presence of the competitive N-addition regioisomer. Other 3-substituted indoles were tested, performing with a similar level of efficiency (entries 7−11). We also evaluated the tolerance of the reaction toward the introduction of substituents at the 5-, 6-, or 7-position of the indole core, and in all cases, the reaction proceeded smoothly (entries 12−16). Changing the R1 substituent at the acyl moiety was also found to be possible, as seen with the excellent performance of the reaction that provided adducts 5q and 5r (entries 17 and 18). In addition, the alkoxy substituent at the ester moiety of the cyclopropane reagent can also be changed from ethoxy to benzyloxy without any negative effect (entry 18). Remarkably, when cyclopropane 1h was employed (entry 19), the reaction took place together with spontaneous hydrolysis/decarboxylation, providing adduct 5s in very high yield.

We also examined the scope of the reaction with respect to the possibility of incorporating different aryl substituents at the cyclopropane core different from the p-methoxyphenyl group used to date (Scheme 2). Almost all substrates tested cleanly furnished the expected cyclocondensation products in excellent yield regardless of the nature of the substituent (compounds 6a−d and 6g) and the position in which this was placed within the aryl substituent (compounds 6e−f). Interestingly, both phenyl-substituted cyclopropane and p-bromophenyl-substituted substrate performed excellently in the reaction (products 6b−c), showing that there is no full need for a strong electron-donating substituent at the cyclopropane scaffold. This event

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**Table 3. Scope of the Reaction: Cyclopropane Reagent**

| entry | 1 | 2 | 3 | 4 | 5 | R1 | R2 | R3 | R4 | Yield (%) |
|-------|---|---|---|---|---|----|----|----|----|---------|
| 1     | 1b| 2a| Sa| 4-NO2C6H4| H | Me | H | 80 |
| 2     | 1b| 2m| Sb| 4-NO2C6H4| H | 4-FC6H4| H | 80 |
| 3     | 1b| 2n| Sc| 4-NO2C6H4| H | 4-MeOC6H4| H | 92 |
| 4     | 1c| 2n| Sc| 4-ClC6H4| H | 4-MeOC6H4| H | 90 |
| 5     | 1d| 2n| Se| Ph | H | 4-MeOC6H4| H | 85 |
| 6     | 1e| 2a| Sf| Ph | CO2Et| Me | H | 94 |
| 7     | 1e| 2g| Sg| Ph | CO2Et| Et | H | 92 |
| 8     | 1e| 2j| Sh| Ph | CO2Et| Bn | H | 81 |
| 9     | 1e| 2l| Sl| Ph | CO2Et| Ph | H | 90 |
| 10    | 1e| 2n| Sj| Ph | CO2Et| 4-MeOC6H4| H | 86 |
| 11    | 1e| 2m| Sk| Ph | CO2Et| 4-FC6H4| H | 82 |
| 12    | 1e| 2b| Sb| Ph | CO2Et| Me | 7-Me| 54 |
| 13    | 1e| 2d| Sm| Ph | CO2Et| Me | 6-Me| 93 |
| 14    | 1e| 2o| Sn| Ph | CO2Et| Ph | 6-MeO| 79 |
| 15    | 1e| 2p| So| Ph | CO2Et| Ph | 5-MeO| 71 |
| 16    | 1e| 2q| Sp| Ph | CO2Et| Ph | 6-F | 87 |
| 17    | 1f| 2l| Sq| 4-ClC6H4| CO2Et| Ph | H | 90 |
| 18    | 1g| 2l| Sr| CO2Bn| Ph | H | 83 |
| 19    | 1h| 2l| St| Ph | H | H | 72 |

*a* All reactions were carried out at 0.05 mmol scale of 1 and 2, using 10 mol % of catalyst in 0.25 mL of toluene until consumption of starting material. *b* Isolated yield after purification. *c* Starting from cyclopropane 1h (R1 = Ph; R2 = CO2EtBu).

**Scheme 2. Use of Cyclopropanes with Different EDG**

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also opens the way to the use of related cyclopropanes without a clear donor–acceptor substitution pattern.

We studied the process in detail by DFT methods to provide a rationale of the observed results. We first studied the reaction of indole 2a with cyclopropyl derivative A as a simplified analogue of substrate 1a. At the same time, we also evaluated the reaction using model cyclopropane B that would lead selectively to the formation of product of general structure 5B. Both attacks to C-2 and N of the indole moiety were considered leading to adducts of type 3A (or 5B) and 4A respectively (Scheme 3). The C-attack consists of two steps, i.e., formation of intermediate IN1A and then IN2A after an H-transfer to recover indole aromaticity. Further cyclization of IN2A and dehydration lead to the final product. The alternative pathway leading to adducts of type 4A involves the N-attack that results in the formation of IN3A (actually the direct product is the enol form; see Supporting Information (SI)) which through concomitant C2-attack to the carbonyl moiety and H-transfer yields IN4A, which after dehydration provides the final product. The calculated energies for these intermediates and the associated TS are also shown in Scheme 3. For both C-2 and N-attacks, the first step in which the nucleophile-induced cyclopropane ring opening takes place is the rate limiting step. For both cases A and B, the C-2 attack is preferred over the N-attack, which showed to be higher in energy, and this would explain the more selective formation of adduct 5B for this particular type of highly activated donor–acceptor cyclopropanes. Several diastereomers can be formed during the process; the lower energy route has been considered in each case (for the complete study, see SI).

In conclusion, we have developed a Brønsted acid catalyzed procedure for performing an unexplored (4 + 2) cyclocondensation between donor–acceptor cyclopropanes and C3-substituted indoles. The methodology described herein presents a broad scope regarding both counterparts of the reaction, providing the corresponding 8,9-dihydropyrido[1,2-α]indoles in good yields and with an excellent level of selectivity. This reactivity pattern is particularly attractive, as it shows the alternative behavior of N-unprotected C3-substituted indoles, in which N and C-2 positions are simultaneously alkylated due to their double nucleophilic character and also forced by the presence of the C3-substituent of the indole that directs the initial alkylation step to the C2-position. Moreover, mechanistic investigations based on computational studies are in concordance with the observed experimental results.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00470.

Experimental procedures, characterization data of all new compounds and copies of 1H and 13C NMR spectra; reaction coordinates, computational details and Cartesian coordinates of all stationary points (PDF)

**Accession Codes**

CCDC 2060969 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

**AUTHOR INFORMATION**

**Corresponding Authors**

Uxue Uria — Department of Organic and Inorganic Chemistry, University of the Basque Country (UPV/EHU), 48080 Bilbao, Spain; orcid.org/0000-0003-0372-7005; Email: uxue.uria@ehu.es

Pedro Merino — Instituto de Biocomputación y Física de Sistemas Complejos (BIFI), Universidad de Zaragoza, 50009 Zaragoza, Spain; orcid.org/0000-0002-2202-3460; Email: pmerino@unizar.es

Jose L. Vicario — Department of Organic and Inorganic Chemistry, University of the Basque Country (UPV/EHU), 48080 Bilbao, Spain; orcid.org/0000-0001-6557-1777; Email: joseluis.vicario@ehu.es

**Authors**

Alesandere Ortega — Department of Organic and Inorganic Chemistry, University of the Basque Country (UPV/EHU), 48080 Bilbao, Spain

Tomás Tejero — Instituto de Síntesis Química y Catalálisis Homogénea (ISQCH), Universidad de Zaragoza, CSIC, 50009 Zaragoza, Spain
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We have previously demonstrated that cyclopropane 1a undergoes ring opening in the presence of chiral phosphoric acids as catalysts: Ortega, A.; Manzano, R.; Uria, U.; Carrillo, L.; Reyes, E.; Tejero, T.; Merino, P.; Vicario, J. L. Catalytic Enantioselective Cloke−Wilson Rearrangement. Angew. Chem., Int. Ed. 2018, 57, 8225−8229.

(11) The structure of 3a was confirmed by X-ray analysis (CCDC 2069069).

(21) When the reaction was carried out with 1 mmol of cyclopropane 1f and indole 2i, adduct 5g was isolated in 83% yield (see the Supporting Information for details).

For details see SI.