Cascade Reactions

Photochemical Approach to the Cyclohepta[b]indole Scaffold by Annulative Two-Carbon Ring-Expansion

Dina Christina Tymann, Lars Benedix, Lyuba Iovkova, Roman Pallach, Sebastian Henke, David Tymann, and Martin Hieresemann* [a]

Abstract: We report on the implementation of the concept of a photochemically elicited two-carbon homologation of a π-donor–π-acceptor substituted chromophore by triple-bond insertion. Implementing a phenyl connector between the slide-in module and the chromophore enabled the synthesis of cyclohepta[b]indole-type building blocks by a metal-free annulative onepot two-carbon ring expansion of the five-membered chromophore. Post-irradiative structural elaboration provided founding members of the indolo[2,3-d]-tropon family of compounds. Control experiments in combination with computational chemistry on this multibond reorganization process founded the basis for a mechanistic hypothesis.

The N-heteroacene cyclohepta[b]indole [1] (1) features the basic scaffold of a variety of man-made pharmaceutically active compounds [2] and natural products [3], for example, alstonlarsine A (2) [4] (Figure 1). To address the challenges associated with the synthesis of cyclohepta[b]indol-type building blocks, a well-diversified portfolio of enabling synthetic methods is already available [5]. Variations of annulation reactions [6] of (m+n)-cycloadditions [7] and of the Cope rearrangement [8] have proven particularly valuable. Notably, however, organic photochemistry has not yet been exploited to access perhydrocyclohepta[b]indole-type building blocks (3).

To complement the existing methodology, we aimed for a fuse–compress–expand sequence to 6,7-dihydro-cyclohepta[b]indol-8(5H)-ones 4 that exploits an unprecedented photochemically triggered two-carbon ring-expansion (Figure 2) [9]. Fusing is accomplished by Sonogashira cross-coupling between o-iodo anilines (5) and terminal alkynes (6), followed by condensation with five-membered cyclic 1,3-dicarbonyl compounds (7) and finalized by N-acylation to deliver photochemistry-competent vinylogous amides 8. The subsequent compress-and-expand phase consists of a photochemically triggered formation of a transient [2+2]-cycloadduct that subsequently collapses to deliver the 6,7-dihydro-cyclohepta[b]indol-8(5H)-one 4; hence, the actual ring-expansion merges excited-state with ground state chemistry to an unprecedented one-pot process.

The experimental procedures and characterization data for the products 8 of the fuse-phase are provided in full detail in the Supporting Information (29 examples). The results of our study on the photochemically triggered two-carbon ring-expansion of 8 are summarized in Tables 1–3. We adopted our previously optimized conditions for the alkyne de Mayo reaction without the necessity of optimization. Hence, solutions of the N-protected vinylogous amides 8a–ab (0.16 mmol) in degassed 2,2,2-trifluoroethanol (TFE, c = 0.03 M) were irradiated in sealable quartz tubes using the low-pressure mercury vapor lamps (Emax = 254 nm) of a commercially available photoreactor.

Reaction times refer to reactor running times. The appearance

Figure 1. Motif (1), Variation (2), and Building Block (3).

Figure 2. Fuse–compress–expand strategy to 6,7-dihydrocyclohepta[b]indol-8(5H)-ones.
of yellow colored reaction mixtures served as an indicator for product formation and progression of conversion was detected by TLC analysis.

Representative examples for aliphatic and aromatic substituents at C-10 were initially screened (Table 1). Ring expansion proceeded for R<sup>1</sup> = octyl- (8a), 4-hydroxybutyl- (8b) and 4-siloxybutyl (8c) to deliver 4a–c in useful yields (85–92%). Somewhat unexpectedly, hydroxymethyl-substitution (8d) triggered decomposition under irradiation. No defined degradation product could be isolated. The nature of the decomposition pathway(s) remains speculative. Fortunately, irradiation of the corresponding silyl ether 8e delivered the ring-expansion product 4e in 86% yield. 2-Aminotolane-derived 8f was susceptible to ring-expansion at prolonged reaction times and delivered the R<sup>1</sup> = phenyl substituted 4f in moderate yield (52%).

For pharmaceutically relevant cyclohepta[<i>b</i>]indoloids, substituent diversification at C-2 is frequently found.<sup>[2]</sup> Consequently, we moved on to study substituent effects for R<sup>2</sup> = H at C-2 and using R<sup>1</sup> = CH<sub>3</sub> at C-10 as a prototype for alkyl substitution (Table 2). Methyl- (8g), trifluoromethyl- (8h) and tert-butyl-substitution (8i) at C-2 were tolerated and 4g–i were isolated in valuable yields (75–91%). 4-Aminobiphenyl-based 8j underwent the ring-expansion slowly and sluggishly to provide 4j (26%) in low yield. Bromo or fluoro substitution enabled access to 4k (83%) or 4l (83%). Suzuki–Miyaura cross-coupling of 4k with phenylboronic acid under carefully optimized conditions delivered 4j (92%); thus 4k may serve as a relay compound for post-ring expansion structural diversification (vide infra).<sup>[10]</sup> π-Donor (R<sup>2</sup> = OCH<sub>3</sub>) and π-acceptor (R<sup>2</sup> = CO<sub>2</sub>Me or CN) substitution allowed the formation of 4m (57%), 4n (86%), and 4o (86%). However, no conversion was observed for R<sup>2</sup> = NO<sub>2</sub> (8p, not depicted).

We proceeded to study substituent effects at C-3 or C-4 for R<sup>2</sup> = H at C-2 and R<sup>1</sup> = CH<sub>3</sub> at C-10. (Table 3). Subjecting vinylogous amides featuring methyl (8q), fluoro (8r), or chloro (8s) substitution at C-3 to the ring-expansion protocol afforded 4q (90%), 4r (83%), and 4s (86%) in valuable yields.
ation of m-aminobenzoic acid derived 8t (R1 = CH3, R2 = CO2Me) required strikingly prolonged irradiation (60 h, 4o: 7 h) and delivered 4t (66%, 4o: 86%) in moderate yield. Degradation was observed for R2 = CH3 (8u); in the event, we speculate that “steric hindrance” interferes with the photochemical compress-phase of the ring-expansion process. 2-Aminonaphthalene-based 8w resisted irradiation (96 h) and was re-isolated (96%), whereas irradiation of the 5,6,7,8-tetrahydro-2-aminonaphthalene-based 8v proceeded reluctantly to afford tetracyclic 4v (50%) in moderate yield. 5-Aminobenzol[d]1,3]dioxole-derived 8x successfully underwent the ring-expansion to yield tetracyclic 4x (52%) in reasonable yield. Finally, we turned tochromo-photoreactivity diversification. Irradiation of N-acetyl derivative 8y yielded the ring-expanded product 4y in 86% yield after only 2.75 h of reactor running time. When irradiating tetronic acid-originated 8z (R1 = CH2, Z = O), no conversion was detected by TLC. Tetramic acid-derived 8aa (R1 = CH2) and 8ab (R1 = Si(CH3)3), however, could be converted into the desired ring-expansion products 4aa (51%) and 4ab (41%) with moderate success.

We are interested in utilizing indole-tropone-fused cyclohepta[bi]indol-8(5H)-ones (indolo[2,3-d]tropones, 10) as scaffold elements for the synthesis of extended N-heteroacenes, N-heterohelicenes, and as building blocks in natural product total synthesis (Table 4). Thus, we explored the dehydrogenation of selected 6,7-dihydro-cyclohepta[b]indol-8(5H)-ones 4. The corresponding lithium enolates were treated with N-tertbutylibenzensulfonimidyl chloride13 to deliver indolo[2,3-d]tropones 9. Purification of the thus-prepared cyclohepta[b]indol-8-ones 9 was complicated by intractable impurities of N-(tert-butyl)-5-phenylthioxohydroxylamine. Alternatively, the enolate of 4k was treated with 1 to deliver Boc-protected 9d (79%); aryloxide 9d is anticipated to serve as a relay compound for scaffold extension as exemplified by Suzuki cross-coupling with potassium vinyltrifluoroborate to afford 9e (70%). Removal of the Boc protecting group delivered 10a (68%) and 10b12 (91%) representing founding members of the indolo[2,3-d]tropone (10) family of compounds.14,15,16

We used experimental and computational studies to gain mechanistic insights into the ring-expansive multibond rearrangement process. Experimentally, irradiation (350 nm) of 8k in the presence of a triplet sensitizer (xanthone) triggered formation of 4k; on the other hand, formation of 4k was suppressed at 254 nm in the presence of a triplet quencher (2,5-dimethylyhexa-2,4-diene).17 On this basis, we assumed a [2+2] cycloaddition on the triplet surface. To gain further mechanistic insights, we performed (TD)DFT studies using the model compound 11 (Figure 3).18,19 Our calculations on the B3LYP/def2-TZVP level of theory predict a vertical excitation of S0–11 to an upper S1-state (+112.6 kcal mol–1) that is followed by internal conversion (IC) to the S1–11 state (n,π* character with respect to the α,β-enone segment) and intersystem crossing (ISC) to the T1–11 state.20 Our computations suggest π,π* character for T1–11 with spin-density being located above and below the α,β-enone segment. Subsequent low-barrier (+4.8 kcal mol–1) 5-exo-dig cyclization to T1–13 via 12 is predicted to be highly endoenergetic (+21.1 kcal mol–1). T1–13 was calculated to be almost isoenergetic to the double bond isomeric T1–14 (–0.5 kcal mol–1); T1–13 is interconnected with T1–14 via a low-barrier transition state (+1.8 kcal mol–1, not depicted). Rapid ISC of T1–14 to S0–14 is followed by an almost barrierless (+1.1 kcal mol–1) and highly exoenergetic (–42.1 kcal mol–1) cyclization via 15 to the (2+2) photocycloadduct 16. According to gas-phase DFT calculations, the π-acceptor substitut-ed cyclobutene segment of 16 is susceptible to a slightly endoenergetic (+2.8 kcal mol–1) concerted bond reorganization via the transition-state 17 (+24.1 kcal mol–1) to afford 18 featuring a trans-α,β-enone moiety.21 The stereochemical result of the modeled conversion of 16 to 18 is in accordance with a bond reorganization proceeding by a conrotatory 4n-electrocyclic ring-opening. Although predicted to be highly exoenergetic, attempts to localize a pathway leading from 18 (or 16) to the model compound 19 for the experimentally observed ring expansion-products by gas-phase computations were futile. The scale of the predicted barrier height (+24.1 kcal) for the conversion of 16 to 18 encouraged experimental studies to identify the [2+2]-cycloadduct. However, efforts to detect the elusive [2+2]-cycloadduct from 8k by (preparative) TLC or by NMR experiments in deuterated solvents failed. The ring-opening was then re-modeled by considering explicit hydrogen-bonding interactions between two molecules of 2,2,2-trifluor-
oethanol (TFE) and the carbonyl oxygen atom of 16 (Figure 3).

Our DFT calculations predict a slightly lower barrier for the weakly endoenergetic electrocyclic ring-opening of 16-2TFE via 17-2TFE (+22.7 kcal mol⁻¹) to 18-2TFE (+3.4 kcal mol⁻¹). Notably, however, consideration of explicit hydrogen bonding interactions opens a low-barrier (⁺11.2 kcal mol⁻¹) pathway for the double-bond isomerization of 18-2TFE to 19-2TFE (⁻35.5 kcal mol⁻¹, not depicted) via 20-2TFE. The transition-state structure 20-2TFE may be best explained as a tightly hydrogen-bonded non-π-resonating α,β-enaminium-enolate zwitterion that we could not locate computationally without considering the transition-state stabilizing interaction with TFE. Experimentally, attempts to perform the two-carbon ring-expansion of 8k in CH₃CN or CH₃OH led to considerably lower isolated yields of 4k (CH₃CN: 61%; CH₃OH: 33%). In both cases 4k was contaminated with unidentified inseparable impurities. To further study the apparent solvent effect, control experiments were run in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). Much to our initial surprise, the resulting isolated yields were considerably lower (HFIP: 66%; TFE: 83%) 4k but free of detectable impurities. We later realized that the comparatively lower yields in HFIP can be attributed to the cleavage of the Boc protecting group in HFIP [22] which slowly proceeds even at ambient temperature without irradiation.

In summary, we reveal a conceptually novel approach to the cyclohepta[b]indole scaffold. Irradiation (254 nm) of modularly assembled vinylogous amides from 2-alkynyl anilines in 2,2,2-trifluoroethanol at ambient temperature triggered an intramolecular one-pot annulative two-carbon ring expansion to deliver 6,7-dihydro-cyclohepta[b]indol-8(5H)-ones. The process merges exit-state [2+2]-cycloaddition with ground-state 4π-electrocyclic ring-opening. Computational chemistry suggests that solvent cooperativity is fundamental to the success of the overall multibond reorganization process. We also report the post-irradiative synthesis and characterization of founding members of the indolo[2,3-d]tetrapone family of compounds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cascade reactions · cyclohepta[b]indole · indole[2,3-d]tetrapone · photochemistry · ring expansion


[12] Deposition numbers 1991297 and 1985305 (9a and 10b) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[13] Structural assignment in solid state and in solution is in accordance with the notion of 9 as cyclohepta[b]indol-8(5H)-one and not as tautomeric cyclohepta[b]indol-8-ol.


[17] For experimental details, see the Supporting Information.

[18] For computational details, see the Supporting Information.


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