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The Witkop Cyclization: A Photoinduced C–H Activation of the Indole System

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C–H activation · medium-sized rings · photochemistry · total synthesis · Witkop cyclization

Investigations of excited-state redox processes have an exceptional impact on the field of organic photochemistry and its application to the synthesis of complex target molecules. In such a photochemical process a single-electron transfer takes place to produce ion-radical intermediates, if the reduction and oxidation potentials, as well as excited-state energies of electron donors and acceptors are chosen appropriately. The Witkop cyclization constitutes an intramolecular variant of such a process, typically with an indole heterocycle as an electron donor. The specific synthetic value of this reaction lies in a C–C bond formation without requiring any prefunctionalization of the indole system. Although this photoreaction has been applied to the total synthesis of natural products, it has still not been used to its full capacity. The following review details synthetic efforts using the Witkop cyclization, and aims to incite further applications of reaction in the synthesis of complex molecular architectures.

1. Introduction

Historically, the Witkop cyclization is the result of an attempted photoreduction of *N*-chloroacetyl tryptophan, and results in a cyclization at the indole 4-position.[1] Since its discovery in 1966, the most important application has been the direct formation of medium-sized lactams across indole heterocycles.[2] The reaction has been studied mostly on hydroxy- and methoxy-substituted aromatic systems with regard to the reaction mechanism and steric factors influencing the reaction behavior. The Witkop cyclization requires electron-rich aromatic rings, which are able to adequately stabilize a radical cation intermediate. Product yields are modest, but the ability to afford medium-sized lactams, including some very strained molecular frameworks, has proven to be of great interest in natural product synthesis.

Beyond any doubt the most valuable feature of the Witkop cyclization comprises C–C bond formation at the C4-position of the indole nucleus. The C4-position is the least reactive site of an indole system and can only be activated by thallium or mercury salts. Otherwise de novo synthesis of the indole core is required. The direct formation of seven-, eight-, or nine-membered ring systems has attracted much attention.[3] We think that the Witkop cyclization is a synthetic process not used to its full capacity, although it has been employed in the synthesis of *Vinca* and *Strychnos* alkaloids,[4,5] as well as indolactam V.[6] In the case of indolactam V, the Witkop cyclization offered the only possibility for a biomimetic synthesis starting from tryptophan.

1.1. Mechanistic Considerations

In terms of the mechanism, it is generally accepted that electron transfer from the excited aromatic core to the α-haloacetamide is taking place, as in both cases (inter- and intramolecular) α-haloacetamides and esters quench the fluorescence of aromatic compounds such as anisole and indole.[7] However, quenching alone is no evidence for a photoalkylation process.

As shown in Scheme 1, an excited complex can undergo one of three processes: 1) nonradiative decay to starting material; 2) homolytic cleavage of the C–Cl bond; 3) electron transfer and heterolytic cleavage of the C–Cl bond. Processes

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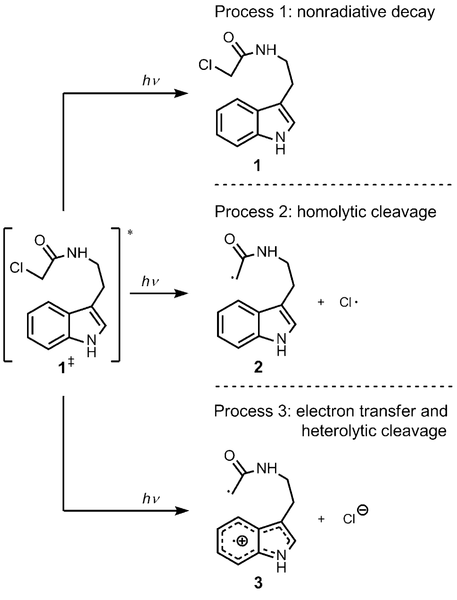


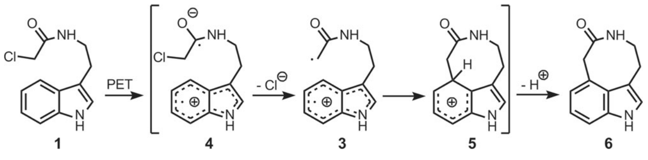
Scheme 1. Possible reaction pathways for photoexcition of α-haloacetamidyl indoles.

(2) and (3) exclusively result in product formation, however, only (3) leads to the desired photocyclization products. Thus structural features restricting either the electron transfer or the heterolytic cleavage of the C–Cl bond are detrimental to good yields.

The most general requirements for structures to undergo the Witkop photocyclization are therefore a sufficiently low reduction potential and a potent leaving group, thus promoting formation of the negative charge and stabilizing the resulting radical.[2] Equally important is the aromatic moiety when stabilizing the radical cation intermediate, where electron-rich aromatic systems tend to give better yields. Another important parameter in this reaction is the solvent. Sundberg et al. used pure water, but as a result of solubility problems, protic solvents or acetonitrile were added. In contrast, the group of Moody found that many reactions gave better results in pure acetonitrile, as water is likely to react with the intermediates. Nonpolar solvents are unfavorable for this reaction because they intercept the electron-transfer mechanism and will result in low yields.

The original literature contains two proposals for the mechanism of the Witkop cyclization. The first comprises a photolytic homolysis of the halogen–carbon bond with subsequent intramolecular aromatic substitution by the free radical at C4 of the indole system. A possible alternative is a concerted intramolecular cyclization with extrusion of the chloride ion.[1]

Currently, the widely accepted mechanism of the Witkop cyclization involves an intramolecular photon-induced electron transfer (PET) from the excited state of the indole chromophore to the chlorocarbonyl moiety, thus generating the intermediate **4** (Scheme 2). Loss of a chloride anion leads to the diradical cation **3**, which undergoes cyclization with the aromatic ring to yield the cation **5**. The final step is rearomatization to the indole system **6** by loss of a proton.



Scheme 2. Accepted mechanism of the Witkop cyclization.

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The Witkop transformation displays a high degree of regioselectivity. Depending on the substitution pattern of the substrate, two different products are mainly obtained. An indole moiety substituted at the C2-position will form the C–C bond at the C3-position to give the 2,3-annulated product (Figure 1). In contrast, an indole system substituted at the C3-position reacts at the C4-position to deliver a 3,4-bridged indole as the major product, and the 2,3-annulated product as a the minor product.

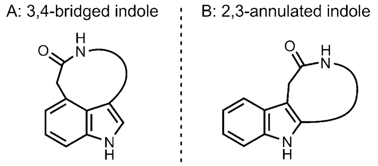


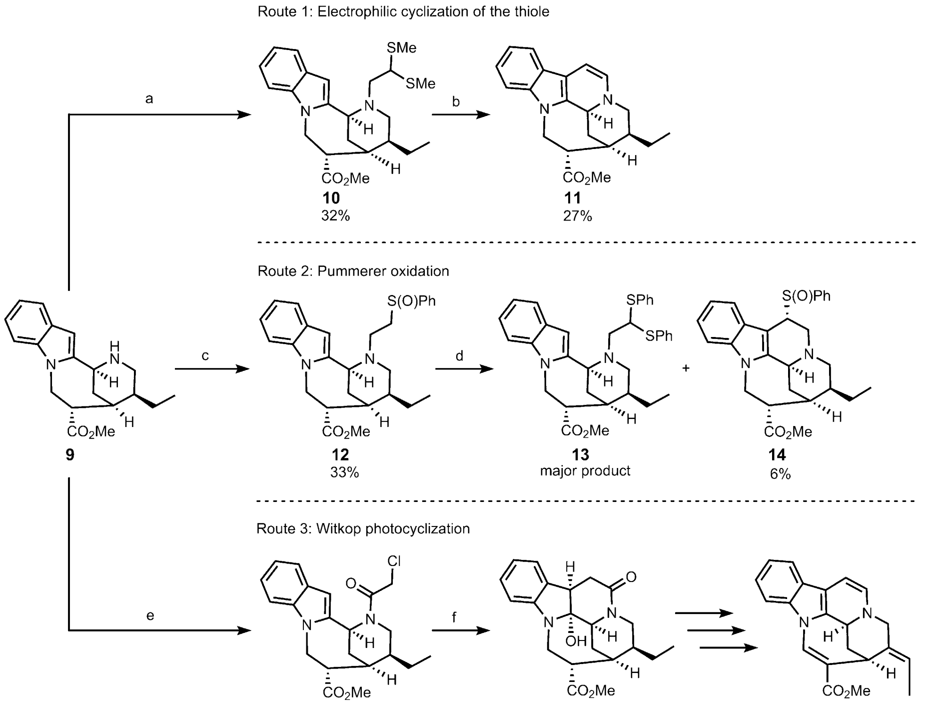
Figure 1. Substitution patterns of the Witkop transformation.

Up to 1983, the Witkop cyclization is well-covered in the literature by Sundberg et al.[2] Therefore, this review highlights and discusses a selection of more recent examples of the Witkop cyclization in the total synthesis of natural products. The results presented herein were arranged according to the substitution pattern of the starting material and underscore the synthetic versatility and power of this transformation, as well as its limitations.

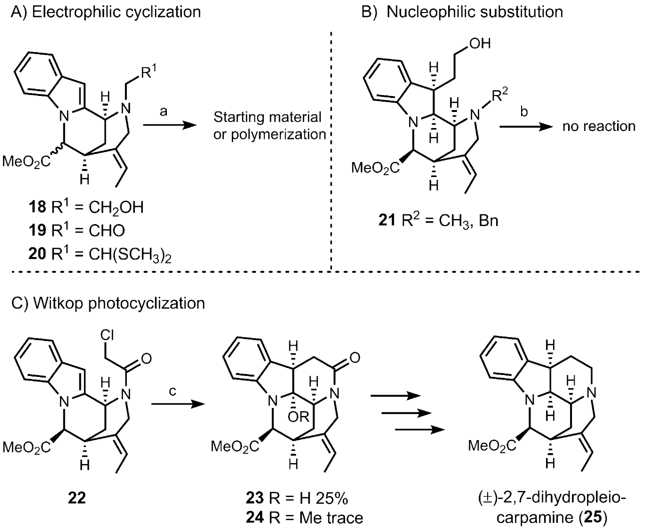
2. Photocyclization of 2-Substituted Indoles

The group of Joan Bosch applied the Witkop cyclization to a number of targets.[8–10] In the construction of the pentacyclic ring system of apogeissoschizine (**17**), three routes were explored for the introduction of the two-carbon bridge at the indole 3-position (Scheme 3).[8] The first route was an electrophilic cyclization of the dithioacetal **10**, and it smoothly proceeded to give **11** in 9% yield over two steps. The second route involved a Pummerer cyclization of the sulfoxide **12**, which was prepared by alkylation of **9** in 33% yield. Unfortunately, the expected product **14** was obtained only in low yield (6%), and the dithioacetal **13** was the major product in this reaction. Alternatively, the Witkop cyclization of the chloroacetamide **15** was investigated, and was synthesized by acylation of **9** (77%). Photocyclization of **15** in 1:1 aqueous methanol in the presence of sodium carbonate gave the pentacyclic product **16** in 14% yield (11% yield over two steps). In all cases the cyclized product was obtained, albeit in varying yields. In general, the authors mention the low stability of substrates and products as an explanation for low yields. For this synthesis the Witkop cyclization was only one possible route among others.

In the first total synthesis of the pentacyclic monoterpenoid (±)-2,7-dihydropleiocarpamine (**25**) by Bosch and coworkers (Scheme 4), the Witkop cyclization turned out to be the method of choice for the successful ring closure of **22** to **23**.[9] The synthesis involves the assembly of the scaffold with the ring closure at the indole 3-position as a late-stage step.



Scheme 3. Reagents and conditions: a) $(SMe)_2CHCHO$, $NaCNBH_3$, MeOH, RT, 16 h; b) DMTSF, CH_2Cl_2; c) $CH_2{=}CHS(O)Ph$, MeOH, reflux, 4 h; d) TMSOTf, DIPEA, CH_2Cl_2, RT, 1 h; e) $ClCH_2COCl$, Et_3N, THF, 0 °C, 1 h; f) hν, 125 W, $\lambda = 254$ nm, Na_2CO_3, MeOH-H_2O 0.5 mg mL^{-1}, N_2, RT, 15 min. DIPEA = diisopropylethylamine, DMTSF = dimethyl(methylthio)sulfonium fluoroborate, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

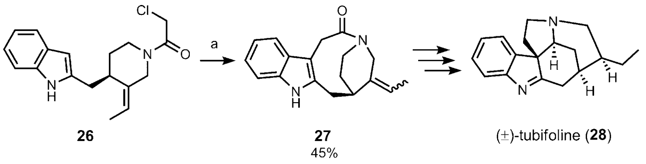


Scheme 4. Reagents and conditions: a) Various conditions. For example, $BF_3 \cdot Et_2O$, $TiCl_4$ or AcOH-HCl; b) Various conditions. For example, MsCl, then NaI, MsCl then $Pd(OH)_2$ or Pd/C; c) hν, $\lambda = 254$ nm, 125 W, Na_2CO_3, $MeOH/H_2O$ (1:1), N_2, RT, 45 min. Ms = methanesulfonyl.

Bosch et al. first tried a direct electrophilic cyclization under acidic conditions. Conversion of the aldehyde into a dithioacetal moiety, similar to the previous presented synthesis, resulted in polymerization (Scheme 4 A).

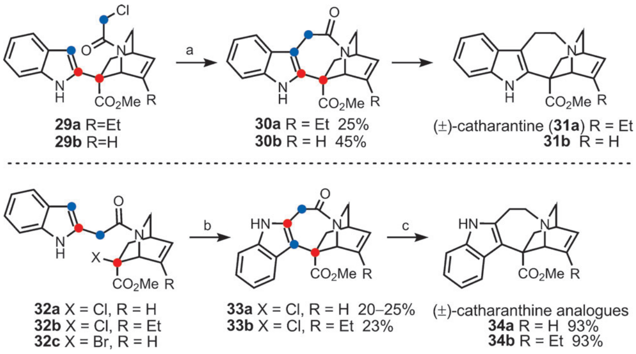
These results promoted study of the construction of this six-membered ring by having a functionalized two-carbon chain at the indole 3-position. The alcohol at the side chain of **21** was converted into a leaving group, which would then be displaced by nucleophilic attack of the nitrogen atom (Scheme 4 B). After this strategy failed, the Witkop photocyclization of the appropriate chloroacetamide **22** was carried out to give the pentacyclic product **23** in 25 % yield and trace amounts of **24** (Scheme 4 C). When aqueous acetonitrile was used as a solvent, **23** was exclusively (15 % yield) formed, whereas **24** was isolated in 10 % yield when pure methanol was used as a solvent.

Bosch and co-workers applied the Witkop cyclization to their enantioselective synthesis of the *strychnos* alkaloid (−)-tubifoline (**28**), as depicted in Scheme 5.[10] The yield of this reaction was 45 % with additional double-bond isomerization (approximately $E/Z = 3:1$). In comparison with other examples from literature this result is remarkable with respect to reaction time, as it was completed in only 15 minutes. When additional substituents were introduced on the piperidine ring, the reaction time was prolonged to nine hours and yields fell to 15 %.[11] Reduction of the double bond to an ethyl group and subsequent irradiation resulted in 20 % yield of cyclized product.[12] Most likely, **26**, containing the ethylene group, adopts a conformation where the two reaction centers are brought into close proximity and therefore leads to increased yields.



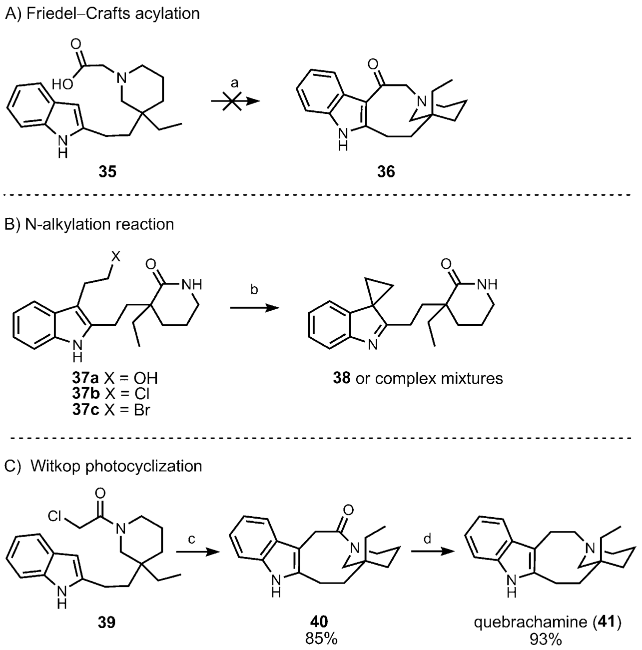
Scheme 5. Reagents and conditions: a) *hν*, Na_2CO_3, $MeOH-H_2O$, N_2, 15 min.

Sundberg et al. exhaustively investigated the efficiency of cyclization for different chain lengths at the C3 indole position.[13] Furthermore, they employed the Witkop cyclization in the synthesis of catharanthine (**31 a**) and its regioisomeric analogues **34 a,b** (Scheme 6).[14] The indole moiety is inversely incorporated into the natural product as compared to its analogues.[15] Photocyclization of **29 a** led to the ring-closed product **30 a** in 25 % yield, thus commencing with a formal total synthesis of (±)-catharanthine. Irradiation of **29 b**, lacking the ethyl side chain at the quinuclidine moiety, delivered **30 b** under the same reaction conditions in 45 % yield. The inverted indole substitution pattern required an α-chloroester instead of an amide in the photocyclization reaction and turned out to be one of the few examples where the substrate is not an α-chloroacetamide. Photocyclization afforded the desired products **33 a** and **33 b** in 20–25 % and 23 % yield, respectively. The corresponding bromo analogue **32 c** did lead to an improved yield.



Scheme 6. Reagents and conditions: a) *hν*, low-pressure mercury lamp (Tungsram 250 W), vycor filter, $NaHCO_3$ (7 equiv), MeOH 1.6 μmol mL^{-1}, N_2, 6 h; b) *hν*, 400 W, vycor filter, $NaHCO_3$ (1.7 equiv), $MeOH/H_2O$ (2.3:1), 2.8 μmol mL^{-1}, N_2, 5 h; c) $NaBH_4$, $BF_3 \cdot EtO_2$, THF.

The total synthesis of (±)-quebrachamine (**41**) by Bajtos and Pagenkopf comprises an example for a high yielding photocyclization process (Scheme 7).[16] Before they carried out a Witkop cyclization on **39**, two other methods were examined, that is a Friedel–Crafts alkylation at the indole 3-position (Scheme 7 A) and an N-alkylation reaction of the 3-substituted indole **37** (Scheme 7 B). Since both approaches did not deliver the desired product, the photoinduced ring-closure methodology was applied and fortunately afforded the desired product **40** (Scheme 7 C). The reaction proceeded smoothly in aqueous ethanol in the presence of sodium carbonate and delivered the product in 85 % yield. In comparison to results of similar Witkop cyclizations, this yield is exceptionally high. The nine-membered transition state enables a more facile alignment of the reacting carbon atoms, and resulted in a less-strained ring than in the previous examples, thus facilitating the reaction. The final product is


A) Friedel–Crafts acylation

B) N-alkylation reaction

C) Witkop photocyclization

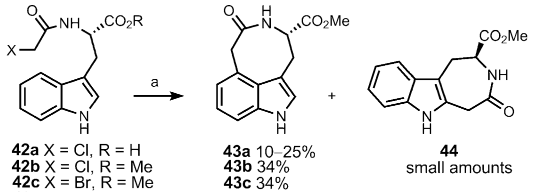
Scheme 7. Reagents and conditions: a) Various Friedel–Crafts acylation conditions; b) **37a**: Mitsunobu conditions, **37b** and **37c**: variety of bases; c) *hν*, EtOH-H_2O, Na_2CO_3; d) $LiAlH_4$, THF, 0°C to reflux, 3 h.

then obtained in a single step by reduction of the carbonyl group with lithium aluminum hydride.

3. Photocyclization of 3-Substituted Indoles

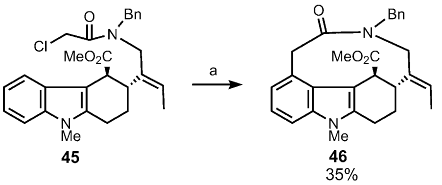
In an indole system the C3-positon displays the highest electron density and is therefore the favored position for attack of an electrophile. The photocyclization of an indole system bearing a chloroacetamide at the 2-position gives the 2,3-annulated product except for a few examples.[13] However, if a 3-substituted indole is subjected to Witkop cyclization conditions, usually a mixture of 3,4- and 2,3-cyclized products in a ratio of roughly 3:1 is obtained.[6]

Irradiation of **42a** at $\lambda = 254$ nm in an aqueous solution and subsequent esterification with diazomethane gave the 3,4-substituted product **43a** in poor yield (10–25%) along with small amounts of the 2,3-fused isomer **44** (Scheme 8). Starting from **42b**, in acetonitrile as the solvent, raised the yield (34%), while switching the wavelength to $\lambda = 350$ nm only gave rise to re-isolated starting material. Changing the halide to bromine or iodine and monitoring the reaction by HPLC showed that the chloro and bromo compounds reacted at comparable rates and gave similar amounts of **43**, although the alternative cyclization product **44** was more prominent in the reaction of the chloro precursor **42b**. In contrast, the iodoacetyl compound decomposed at a slower rate and gave rise to a number of unidentified products.



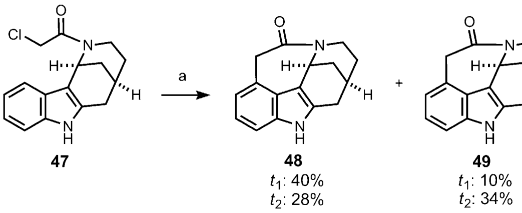
Scheme 8. Reagents and conditions: a) **42a**: *hν*, H_2O; **42b–d**: *hν*, MeCN.

The example in Scheme 9 showcases a macrocyclization of the tricyclic chloroacetamide **45** to form the 10-membered lactam **46**. Irradiation of **45** in aqueous methanol afforded **46** in 35% yield as the only isolable product. The ^{1}H NMR spectra of the macrolactam indicated two conformational states in solution, with a high-energy barrier of interconversion ($T_c = 120$°C). This behavior is quite common for indole annulated macrolactams.[17] Furthermore, this experiment confirms that photocyclization of chloroacetamides to the 3-position is prohibited by the presence of a substituent at this position. Therefore, the Witkop reaction is not suited for quaternization/dearomatization at the C3 indole position.



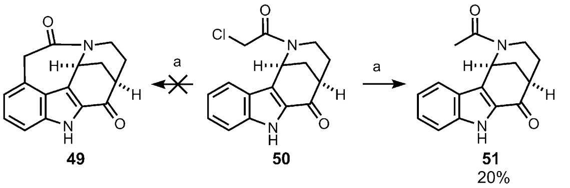
Scheme 9. Reagents and conditions: a) *hν*, MeOH-H_2O.

Another example for a 2,3-annulation process is seen with the tetracycle **47**. Irradiation for 45 minutes delivered the pentacyclic compound **48** in 40% yield (Scheme 10).[18] The 2-acylindole **49** was isolated as a by-product in 10% yield. Irradiation of the starting material for 200 minutes changed the yields of the pentacyclic compounds **48** and **49** to 28% and 34%, respectively. The photo-oxidation of 2,3-dialkylindoles into the corresponding 2-acylindoles under aerobic conditions, via 3-hydroxyindolenine intermediates is, a well-known process and was described by Nakagawa and co-workers.[19]



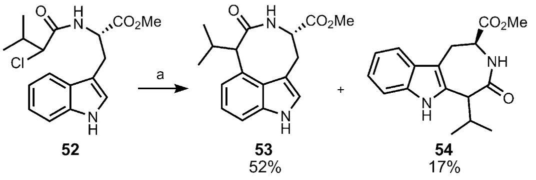
Scheme 10. Reagents and conditions: a) *hν*, MeOH, K_2CO_3, $t_1 = 45$ min, $t_2 = 200$ min.

Bosch and co-workers attempted a Witkop cyclization on the keto compound **50**, but instead of obtaining the desired pentacycle **49**, the dechlorination product **51** was isolated in 20% yield (Scheme 11). The different behavior of this compound under photolytic conditions was explained by the deactivation caused by the carbonyl group conjugated with the indole system.



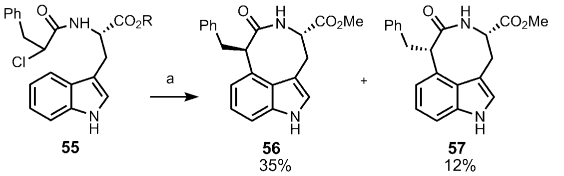
Scheme 11. Reagents and conditions: a) *hν*, MeOH, K_2CO_3.

The examples highlighted so far lead to the conclusion that mainly two factors govern the regioselectivity in this photochemical process. One is the geometric alignment of the aromatic ring and the chloroacetamide group, and the other is the distribution of electron density on the aromatic ring. Scheme 12 reflects this regioselectivity where irradiation of the α-substituted chloroamide **52** delivered the eight-membered 3,4-indole **53** (52%), and the seven-membered 2,3-indole **54** (17%). The regiochemistry may also be rationalized by charge distribution of the indole radical. Application of the SFC-MO theory shows an approximate correlation of the singly unoccupied molecular orbital electron density with regioisomer distribution.[20]



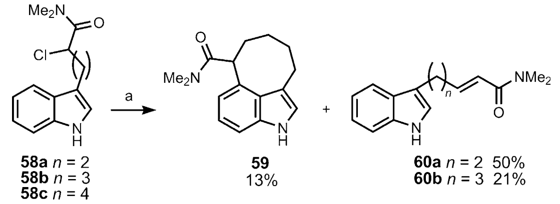
Scheme 12. Reagents and conditions: a) *hν*, MeCN.

As can be seen from Scheme 13, the reaction tolerates substituents at the α-position of the chloroamide. Irradiation of **55** gave a 3:1 mixture of the diastereomers **56** and **57** in 47% yield. This tolerance enables the synthesis of azocino-indoles (related to serotobenine) using the Witkop process.[21]



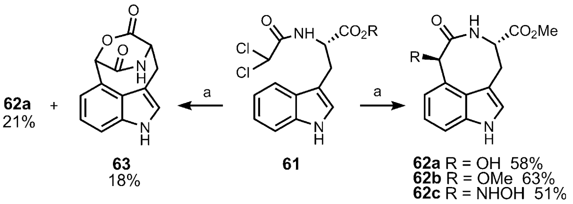
Scheme 13. Reagents and conditions: a) *hν*, MeCN.

In contrast to the examples presented so far, which yielded a medium-sized lactam ring, Moody and co-workers carried out detailed mechanistic studies of the Witkop cyclization leading to 3,4-cyclized carbocyclic products, with the amide functionality as a substituent on the medium sized ring.[22] A competing elimination reaction occurs to form the compounds **60** instead. The reaction pathway depends on the chain length, as can be seen in Scheme 14. Any chain length below $n=4$ results exclusively in elimination products. Irradiation of **58b** ($n=4$) did indeed result in the desired photocyclization and the cyclooctadiene **59** was formed, albeit in poor yield.



Scheme 14. Reagents and conditions: a) *hν*, MeCN.

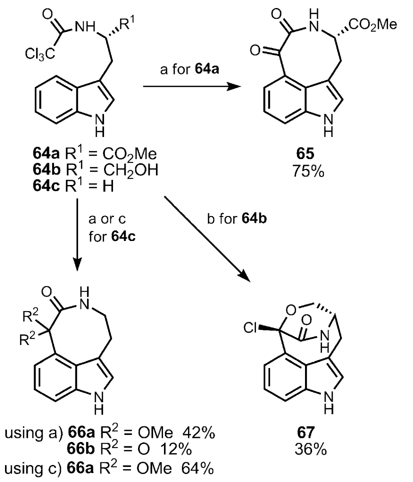
Moody and co-workers also investigated dichloroacetyl tryptophan derivatives as substrates, where the additional chloride would provide the opportunity for further functionalization of the product. Irradiation of **61** at $\lambda = 254$ nm in acetonitrile gave **62a** in 58% yield (Scheme 15), which is a major improvement compared to conversion of **42a** into **43a** (10–25% yield, Scheme 8). The alcohol in the product is probably formed during workup. In the presence of other nucleophiles such as methanol or hydroxylamine, the corresponding substituted compounds **62b** and **62c** were formed. Photocyclization in aqueous media gave **62a** and **63** in a 1:1 ratio. The increased yields of **62a–c** may be attributed to the higher stability of the chloroacetamido radical as opposed to the unsubstituted radical, thus resulting in a higher selectivity and smaller amounts of undesired side products.



Scheme 15. Reagents and conditions: a) *hν*, MeCN; then H_2O, MeOH or NH_2OH; b) *hν*, MeCN-H_2O.

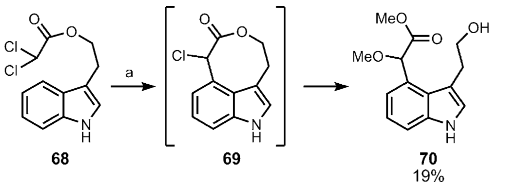
Since one additional chloride had a positive effect on the yield, the photocyclization of *N*-trichloroacetyl tryptohphan was expected to give even better yields and a better regioselectivity for the 4-position of the indole system. Indeed, cyclization of **64a** in aqueous acetonitrile furnished **65** in 75% yield (Scheme 16). When the corresponding tryptophanol derivative **64b** was irradiated, the cyclic chloro ether **67** was the only product isolated (36% yield). The photocyclization of *N*-trichloroacetyl-tryptophan methyl ester was also extended to the corresponding tryptamine derivate. When the reaction was carried out in methanolic acetonitrile the major product was **66a** (42%) along with ketoamide **66b** (12%). When the same reaction was carried out in aqueous acetonitrile, **66a** was the only product and was isolated in 64% yield.

Additional investigations of di- and trichloroacetyl derivatives of tryptophol and homotryptophol as substrates in the photocyclization were described by Moody and co-workers.[23] Initial photocyclization studies of dichloroacetyl tryptophol in acetonitrile were disappointing since no product could be



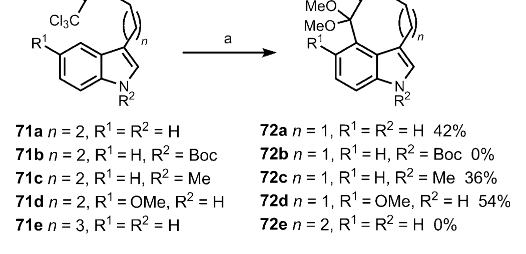
Scheme 16. Reagents and conditions: a) *hν*, MeCN-MeOH; b) *hν*, MeCN; c) *hν*, MeCN-H_2O.

isolated. However, in the presence of MeOH as a nucleophile the 3,4-substituted indole **70** was obtained in 19% yield, and presumably arises from initial photocyclization product **69** by nucleophilic displacement of chloride by methanol and subsequent methanolysis of the eight-membered lactone (Scheme 17).



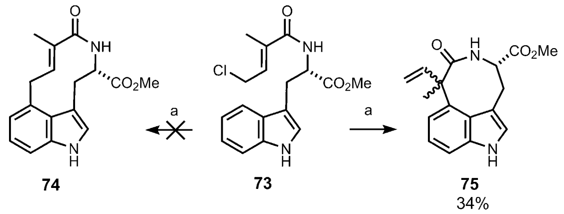
Scheme 17. Reagents and conditions: a) *hν*, MeCN/MeOH (4:1).

Since additional chlorine atoms were beneficial for augmentation of yields in the previously presented cases, di- and trichloroacetyl moieties were investigated with tryptophanols (Scheme 18). Likewise, an increase in product yield could be observed, as irradiation of **71a** in methanolic acetonitrile furnished the pyrrolobenzoxocine **72a** in 42%. Placing an electron-withdrawing substituent, such as a Boc-group (**71b**), on the indole nitrogen atom prevents the photocyclization and the only isolated product was *N*-Boc-tryptophanol after cleavage of the ester moiety. The N-methyl derivate **71c** successfully cyclized to give **72c** in 36% yield, and further increase of the electron density with an electron-donating group gave the tricycle **72d** in 54% yield. Attempts to form the nine-membered bridged indole lactone **72e** from a three-carbon atom chain of **71e** failed. The only isolable product after irradiation was homo-tryptophanol.



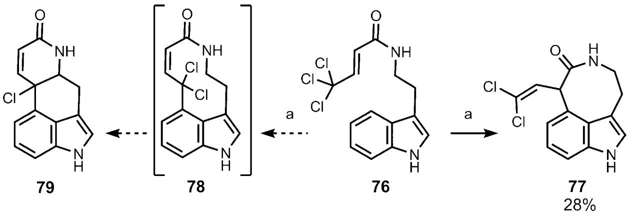
Scheme 18. Reagents and conditions: a) *hν*, MeCN/MeOH (4:1). Boc = *tert*-butoxycarbonyl.

Endo and co-workers investigated a vinylogous Witkop cyclization reaction with the α,β-unsaturated chloroamide **73** (Scheme 19). Irradiation of **73** in dry acetonitrile at room temperature provided the eight-membered lactam **75** in a 1:1 mixture of diastereomers in 34% yield. Hence, it was not possible to form the desired 10-membered lactam **74**.[24] Presumably, the initially generated primary allylic radical isomerizes to the more stable tertiary position of the molecule and gives rise to the eight-membered ring instead of the 10-membered macrocycle.



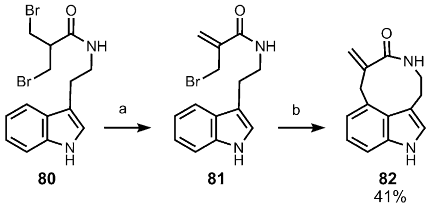
Scheme 19. Reagents and conditions: a) *hν*, MeCN.

Based on these facts, Mascal and co-workers examined a vinylogous Witkop cyclization with the unsaturated trichloroamide **76** (Scheme 20). The ultimate goal of this work was to gain efficient access to the ergoline skeleton **79**. However, irradiation of the cyclization precursor **76** exclusively provided the eight-membered tricycle in 28% yield.[25] Hence, the experiment is consistent with the observation of Endo et al..



Scheme 20. Reagent and conditions: a) *hν*, MeCN.

Because of this result, Mascal and co-workers chose to the new test system **81**, which should undergo vinylogous Witkop cyclization (Scheme 21). The methacrylamide **81** was prepared from **80** by elimination of hydrogen bromide. Irradi-

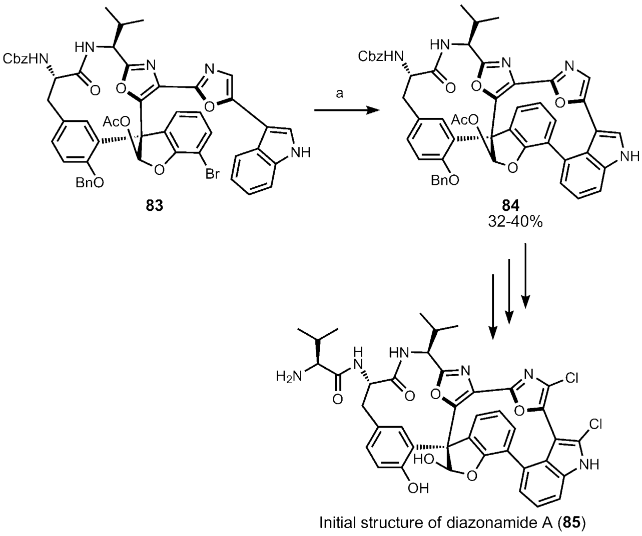


Scheme 21. Reagents and conditions: a) NaOH; b) *hν*, MeCN.

ation of **81** in acetonitrile delivered the desired nine-membered lactam **82** in a moderate 41 % yield.

3.1. Cyclization of 3-Substituted Indoles in Total Synthesis

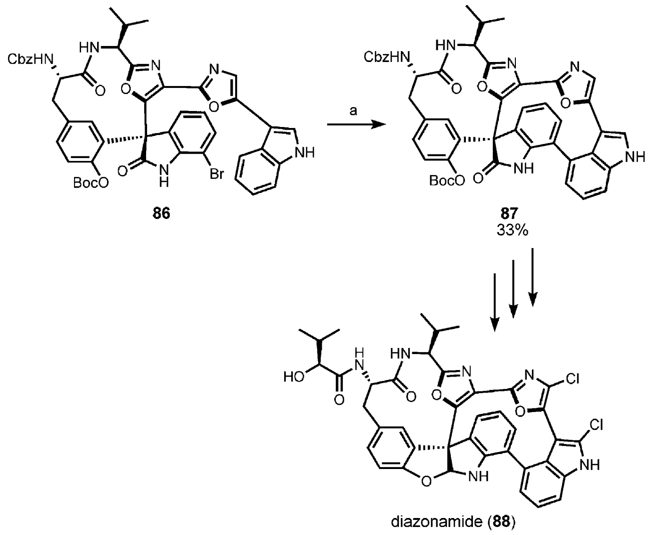
Harran and co-workers used the Witkop cyclization as a key step in their synthesis of the originally proposed structure of diazonamide A (**85**).[26] Irradiation of **83** in a mixture of methanol and water, lithium acetate, and epichlorohydrin afforded the macrocycle **84** in 32–40 % yield (Scheme 22). Functional group manipulations completed the synthesis of diazonamide A (**85**), which unfortunately turned out to be misassigned.



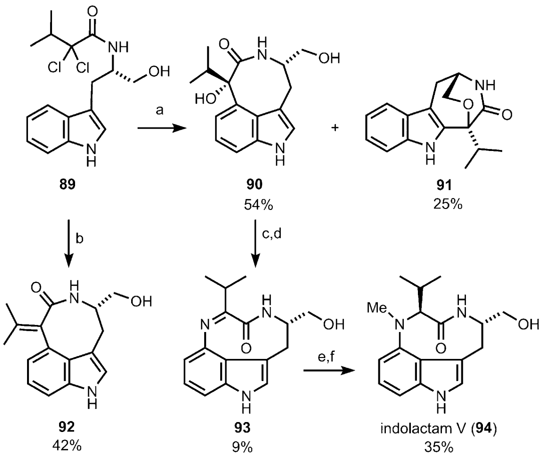
Scheme 22. Reagents and conditions: a) *hν*, 2 equiv LiOAc, 3 equiv epichlorhydrin, MeOH/H_2O (3:1). Cbz = benzyloxycarbonyl.

With the revised structure of diazonamide A (**88**) in hand, Nicolaou and co-workers envisioned a total synthesis in which they used a Witkop cyclization to close the 14-membered macrocycle of this corrected structure (Scheme 23).[27] Applying photocyclization conditions, similar to those used by Harran and co-workers, to **86** afforded the macrocycle **87** in 33 % yield together with 50 % of unreacted starting material. Several more steps lead to the correct structure of diazonamide A (**88**).

Another application of the Witkop cyclization is demonstrated in the total synthesis of indolactam V (Scheme 24).[28] Photocyclization of the dichloroamide **89** in aqueous acetonitrile delivered the two diastereoisomers of **90** (54 %) in a 4:1 ratio together with the tetracyclic indole **91** in 25 % yield. By contrast, irradiation of **89** in dry acetonitrile afforded the unsaturated lactam **92** in 42 % yield. Substitution of the tertiary hydroxy group of **90** with sodium azide gave after subsequent irradiation the indolactam skeleton **93**. Reduction of the imine moiety and methylation of the nitrogen atom provided the natural product indolactam V (**94**).



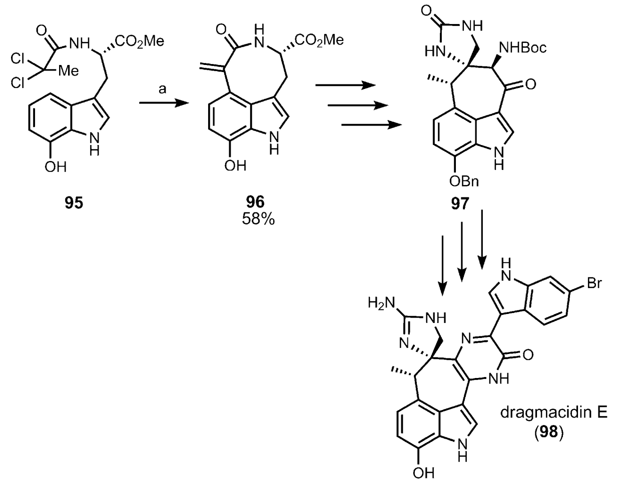
Scheme 23. Reagents and conditions: a) *hν*, 2 equiv LiOAc, 3 equiv epichlorhydrin, MeOH/H_2O (3:1).



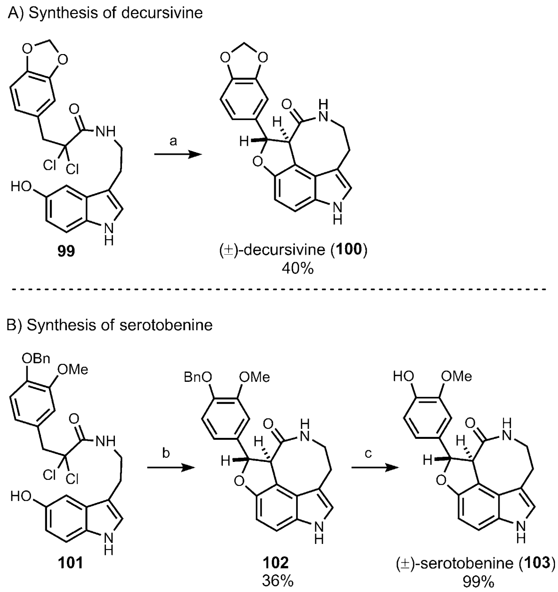
Scheme 24. Reagents and conditions: a) *hν*, aq. MeCN; b) *hν*, MeCN; c) NaN_3, TFA, $HCCl_3$; d) *hν*, MeCN; e) $NaBH_3CN$, MeOH; f) MeI, $NaHCO_3$, MeOH. TFA = trifluoroacetic acid.

The total synthesis of dragmacidin E (**98**) presented by Feldman et al. relies on the Witkop cyclization of substrate **95** to furnish the lactam **96** (Scheme 25).[29] As previously demonstrated by the group of Moody, Feldman et al. used a dichloroacetylated tryptamine derivate (**95**) to introduce the methyl group later on in the synthesis. The lactam **96** was obtained in 58 % yield. Its alkene moiety was presumably obtained from a photochemical dehydrochlorination/elimination reaction. The synthesis was continued by the transformation of the cyclooctanoid skeleton into the cycloheptanoid bridged system by a Dieckmann ring-closing/ring-opening sequence and subsequent functional group interconversions, and installation of the urea moiety to the tetracycle **97**. Condensation of **97** with the bromoindole building block paved the way to conclude the synthesis of dragmacidin E (**98**).

Jia and co-workers used a dichloro substrate for a Witkop cyclization in the total synthesis of (±)-decursivine (**100**) and



Scheme 25. Reagents and conditions: a) *hν*, MeCN, RT, 3 h.



Scheme 26. Reagents and conditions: a) *hν*, 5 equiv Li_2CO_3, MeCN/H_2O (10:1), 4.5 μmol mL^{-1}, RT; b) *hν*, LiOAc, MeCN/H_2O (5:1), RT 4 h; c) H_2, 10% Pd/C, THF/MeOH (2:1), RT, 3 h.

(±)-serotobenine (**103**; Scheme 26).[21] Based on the result from the groups of Moody and Feldmann, Jia et al. envisioned a photocyclization cascade reaction where the resulting alkene would be part of a Michael acceptor and thus undergo an intramolecular oxa-Michael addition. It was revealed that both solvent and base played an important role, but after optimization of the reaction the desired product (±)-decursivine (**100**) could be obtained as initially planned in one step from the dichlorotryptamine derivative **99** in 40% yield. To obtain (±)-serotobenine (**103**) subsequent cleavage of the benzyl group was necessary.

4. Conclusion

In summary, the average yields for the Witkop cyclization range from 30 to 55%. Byproducts are rarely reported but originate from photochemical dehalogenation processes to β-elimination reactions of HCl for α-chloroamides, which are more complex than α-chloroacetamide. High yields tend to be rare for this reaction, although certain examples have been reported. Nevertheless, this reaction provides a short and direct access to complex polycyclic structures, and is therefore of high synthetic value, especially since substrates for this reaction are generally easy to synthesize. Alternative strategies are most often more laborious, require a multistep sequence, and have lower overall yields. Therefore, the Witkop cyclization is a viable synthetic tool for the synthesis of indole-containing natural products.

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