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Synthesis of 3,3′-Disubstituted Indolenines Utilizing the Lewis Acid Catalyzed Alkylation of 2,3-Disubstituted Indoles with Trichloroacetimidates

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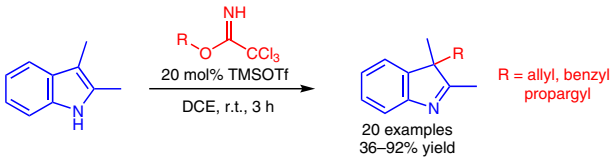

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Abstract Trichloroacetimidates function as effective electrophiles for the selective C3-alkylation of 2,3-disubstituted indoles to provide 3,3′-disubstituted indolenines. These indolenines are common synthetic intermediates that are often utilized in the synthesis of complex molecules. Effective reaction conditions utilizing Lewis acid catalysts have been determined, and the scope of the reaction with respect to indole and imidate reaction partner has been investigated. This chemistry provides an alternative to base promoted and transition-metal-catalyzed methods that are more commonly utilized to access similar indolenines.

Key words indole, trichloroacetimidate, alkylation, indolenine, Lewis acid, catalysis

The dearomatization of indoles is a powerful strategy for the synthesis of 3,3′-disubstituted indolenine intermediates.[1] Similar indolenine substructures are present in many complex molecules, like strictamine,[2] koumine,[3] and tubifoline[4] (Figure 1). In addition, many indoline-containing structures (like aspidophylline A[5] and communesin B[6]) appear readily accessible from similar indolenine substructures. Given their prevalence in alkaloids, it is not surprising that a number of techniques have been reported for the intermolecular C3-alkylation of 3-substituted indoles with benzyl, allyl, and propargyl electrophiles to form C3-quaternary indolenines. Typically these methods rely on the use of strong base to activate the indole by deprotonation[7] or on the use of a transition-metal catalyst to activate the electrophile.[8] More recently work has turned to utilizing acid catalysts to perform similar transformations.[9] Our recent studies on substitution reactions with trichloroacetimidate electrophiles[10] led us to investigate the propensity of electron-rich aromatic systems like indoles to undergo dearomatization/alkylation reactions with trichloroacetimidate electrophiles to access 3,3′-disubstituted indolenines. Imidates typically function as alkylating agents under mild acidic conditions, and the use of imidates in the alkylation of indoles would facilitate the introduction of a wide variety of allyl, benzyl, and propargyl groups from the corresponding imidate, which are readily available from the respective alcohol.

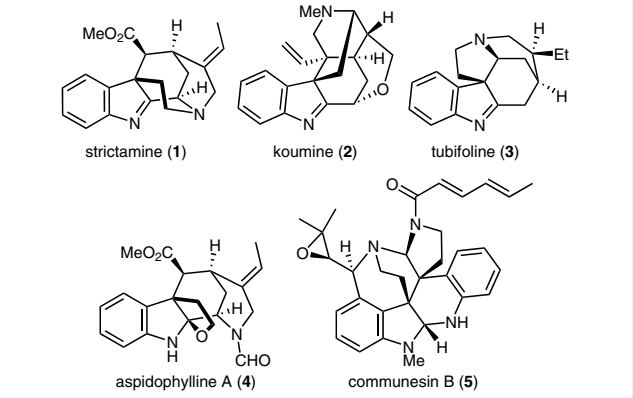
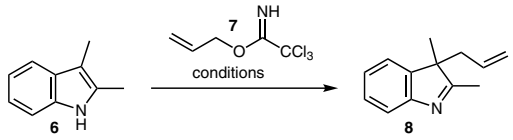


Figure 1 Selected 3,3′-disubstituted indolenine and indoline natural products

Trichloroacetimidates have been shown to be effective electrophiles in Friedel–Crafts-type alkylation reactions with substituted benzene rings as nucleophiles.[11] Indoles provide an interesting heterocyclic regime to explore, as they may undergo alkylation at different sites depending on their substitution pattern. A number of Friedel–Crafts alkylation reactions between imidates and indoles have been previously reported,[11g,h,12] but there have been no reports on the use of imidates to form 3,3′-indolenine structures. Indole itself provides C3-alkylation products with a variety of imidates.[11g,h] In cases where the indole C3-position is substituted C2-alkylation usually predominates,[12d] although in some cases N-alkylation is observed.[12c]

In order to evaluate the potential of trichloroacetimidates as electrophiles in the formation of 3,3′-disubstituted indolenines, the Friedel–Crafts reaction of 2,3-dimethylindole with allyl trichloroacetimidate was investigated (Table 1). A number of Brønsted and Lewis acid catalysts were evaluated to facilitate the transformation. TMSOTf was found to be the most effective catalyst, with nonpolar halogenated solvents like CH_2Cl_2 and DCE being found to be the optimal reaction medium. Performing the transformation with lower loadings of TMSOTf led to significantly slower reactions and lower conversions, so 20 mol% was used in subsequent experiments. Shorter reaction times also led to incomplete conversion (Table 1, entry 12). In order to rule out triflic acid as a catalyst in the alkylation with TMSOTf, the reaction was performed in the presence of 2,6-di-*tert*-butyl-4-methylpyridine, which is known to bind Brønsted acids but not Lewis acids.[13] A 67% yield was obtained in this case, implicating TMSOTf as the operative catalyst in the reaction.

Table 1 Optimization of Reaction Conditions

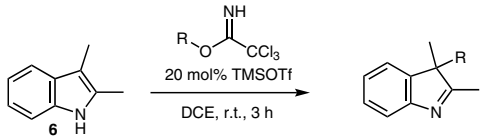


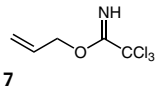
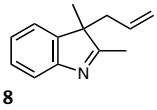
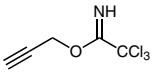
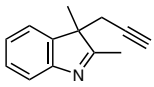
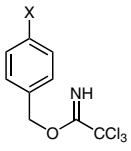
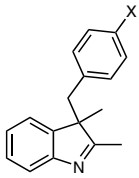
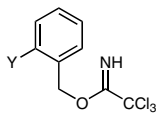
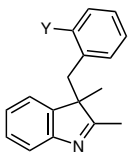
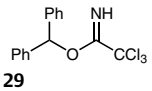
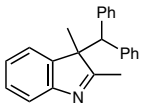
Entry	Conditions	NMR yield (%)[a]	Yield (%)[b]
1	20 mol% PPTS, DCE, rt, 21 h	5[c]	–
2	20 mol% CSA, DCE, rt, 21 h	10[c]	–
3	20 mol% TfOH, DCE, rt, 21 h	–	50
4	20 mol% $Cu(OTf)_2$, DCE, rt, 21 h	–	14
5	20 mol% $ZnBr_2$, DCE, rt, 21 h	28[c]	–
6	20 mol% $BF_3{\cdot}OEt_2$, DCE, rt, 21 h	–	5
7	20 mol% TMSOTf, DCE, rt, 21 h	–	70
8	20 mol% TMSOTf, CH_2Cl_2, rt, 21 h	–	69
9	20 mol% TMSOTf, $PhCF_3$, rt, 21 h	–	9
10	20 mol% TMSOTf, THF, rt, 21 h	–	21
11	20 mol% TMSOTf, DCE, rt, 3 h	–	74
12	20 mol% TMSOTf, DCE, rt, 1 h	76[c]	–
13	20 mol% TMSOTf, DCE, rt, 3 h	–	67[d]

[a] Yield as estimated by crude ^1H NMR analysis against an external standard (mesitylene).
[b] Isolated yield.
[c] Some starting material still remained.
[d] 20 mol% 2,6-di-*tert*-butyl-4-methylpyridine was added.

With conditions in hand that provide good yield of the desired indolenine product, the transformation was evaluated with regard to trichloroacetimidate alkylation partner (Table 2). The propargyl imidate **9** appeared to be a less reactive substrate under these reaction conditions, and required both heating the reaction to reflux and the addition of a second aliquot of 20 mol% of TMSOTf after 24 hours, and then another 24 hours of reaction time at reflux for the consumption of starting material (Table 2, entry 2). Using

Table 2 Alkylation of 2,3-Dimethylindole with Trichloroacetimidates



Entry	Imidate	Product	Yield (%)[a]
1	 **7**	 **8**	74
2	 **9**	 **10**	67[b]
3	 **11** X = NO_2	 **12** X = NO_2	92[c]
4	**13** X = CN	**14** X = CN	71[d]
5	**15** X = CF_3	**16** X = CF_3	69
6	**17** X = Cl	**18** X = Cl	58
7	**19** X = H	**20** X = H	50[c]
8	**21** X = Me	**22** X = Me	47
9	**23** X = OMe	**24** X = OMe	45
10	 **25** Y = NO_2	 **26** Y = NO_2	43[d]
11	**27** Y = Cl	**28** Y = Cl	52[e]
12	 **29**	 **30**	71

[a] Isolated yield.
[b] Reaction was heated to reflux for 24 h, then another 20 mol% of TMSOTf were added, and the reaction was refluxed for another 24 h prior to work-up.
[c] Reaction was stirred at rt for 48 h.
[d] Reaction was heated to reflux for 24 h.
[e] Reaction was heated to reflux for 6 h.

these modified conditions a 67% yield of the propargyl product **10** could be isolated. Attention was then turned to benzylic trichloroacetimidates. Benzylic imidates with electron-withdrawing groups on the aromatic ring gave significantly higher isolated yields of product than more electron-rich systems (Table 2, entries 3–6). This is unusual as typically imidates with electron-releasing groups are more reactive alkylating agents in esterification and etherification reactions.[14] The alkylations with the more electron-rich benzylic trichloroacetimidates were also more difficult to purify and seemed to provide more side products than alkylations with electron-poor benzylic trichloroacetimidates (Table 2, entries 8 and 9). Careful examination of the ^{1}H NMR analysis of the crude reaction mixture showed that mixtures of the undesired Friedel–Crafts alkylation at the indole 5- and 7-positions made up the bulk of these side products. The formation of these unwanted products and complications with purifying them away from the desired 3,3′-indolenine product led to the lower isolated yields. Substitution at the *ortho* position of the benzylic trichloroacetimidates also provided lower isolated yields, perhaps for steric reasons (Table 2, entries 10 and 11). Adding substitution at the benzylic carbon of the imidate was well tolerated as shown by the use of imidate **29**, which provided the 3,3′-indolenine product **30** in 71% yield (Table 2, entry 12).

The effect of the structure of the indole nucleophile on the alkylation was then explored, with a number of different indoles being used in the alkylation reaction with allyl trichloroacetimidate **7** (Table 3). Addition of a chlorine atom at the 5-position of the indole slowed the reaction significantly, with the reaction mixture needing to be heated to reflux to access a reasonable reaction rate. Still, a 60% yield of the indolenine **32** could be isolated. The slower reaction was attributed to the reduced nucleophilicity of the indole due to the electron-withdrawing chlorine atom.

Table 3 Alkylation of Allyl Trichloroacetimidate with Differentially Substituted Indoles

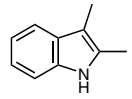
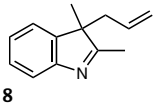
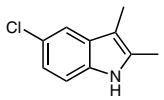
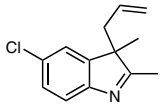
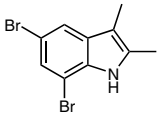
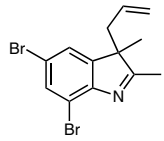
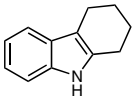
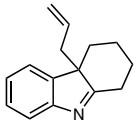
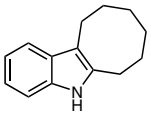
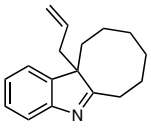
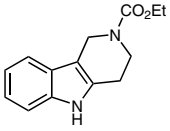
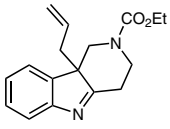
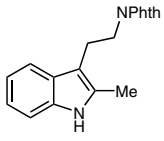
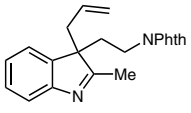
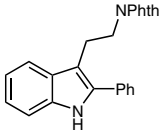
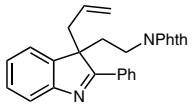
Entry	Indole	Product	Yield (%)[a]
1	 **6**	 **8**	74
2	 **31**	 **32**	60[b]

Table 3 (continued)

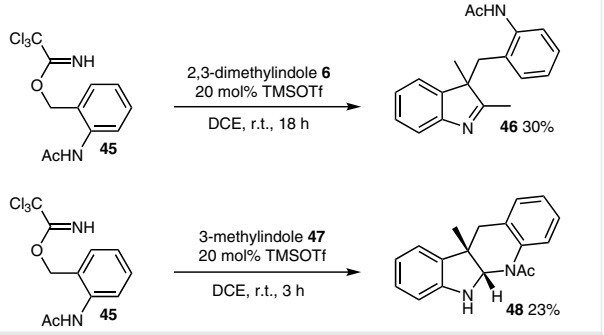
Entry	Indole	Product	Yield (%)[a]
3	 **33**	 **34**	81[c]
4	 **35**	 **36**	42
5	 **37**	 **38**	47[d]
6	 **39**	 **40**	54
7	 **41**	 **42**	52
8	 **43**	 **44**	36[e]

[a] Isolated yield.
[b] Reaction was heated to reflux for 3 h.
[c] Reaction was heated to reflux for 2 h.
[d] Reaction was heated to reflux for 8 h.
[e] Reaction was heated to reflux for 18 h.

Dibromoindole **33** also required heating (Table 3, entry 3), but provided the desired product **34** in 81% isolated yield. This increase in yield is rationalized by the bromine atoms protecting the indole benzene ring from competing alkylation reactions. Indoles with carbocyclic rings tethered between the indole 2- and 3-positions were also evaluated (Table 3, entries 4–6). These systems gave more moderate conversions, likely due to steric factors. The protected γ-carboline derivative **39** underwent selective alkylation at the indole 3-position in 54% yield. A phthalimide protected 2-methyltryptamine was also utilized as a substrate, pro-

viding the alkylated product in 52% yield (Table 3, entry 7). Increasing the size of the substituent at the indole 2-position resulted in a decrease in yield, as shown with the 2-phenyl indole **43** (Table 3, entry 8).

The application of this method in the synthesis of the core system of the communesin natural products[15] was also undertaken (Scheme 1).[16] This route takes advantage of imidate **45**, which was synthesized from the commercially available 2-aminobenzyl alcohol in two steps (see Supporting Information for details). Subjecting imidate **45** and 2,3-dimethylindole to the alkylation reaction conditions resulted in the formation of indolenine **46**, but no cyclization of the pendant acetamide on the imine was observed. This may be due to the enhanced stability of the indolenine of **46** due to the presence of a methyl group at the 2-position. Switching to 3-methylindole **47** as a nucleophile to avoid this issue gave indoline **48**, where the pendant acetamide group cyclized into the imine to provide the core tetracyclic ring system of communesin. While currently the yield of this transformation is moderate (23%), with further optimization similar reactions may find use in accessing communesin analogues or similar structures.



Scheme 1 Synthesis of the communesin core ring system

In closing, reported herein are conditions where trichloroacetimidates function as electrophiles for the selective C3-alkylation of 2,3-disubstituted indoles in the presence of a Lewis acid catalyst.[17] Allyl trichloroacetimidate served as an excellent electrophile to provide the C3-allyl indolenine product in good yields with a number of substituted indoles. The scope of the reaction with electron-poor and electron-rich primary benzylic trichloroacetimidates has also been investigated. In the future chiral Lewis acid catalysts may be explored to access enantioenriched indolenine products. This protocol may be useful in accessing complex 3,3′-indolenine-containing structures. Further studies on the reactivity of differentially substituted indoles with trichloroacetimidates are under way and will be reported in due course.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588491.

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(17) **Representative Procedure for C3-Alkylation of 2,3-Disubstituted Indoles with Trichloroacetimidates**

In a flame-dried flask allyl trichloroacetimidate **7** (121 mg, 0.60 mmol) was dissolved in 4 mL of anhydrous DCE. 2,3-Dimethylindole (**6**, 130 mg, 0.90 mmol) was then added followed by freshly distilled TMSOTf (20 mol%, 27 µL, 0.12 mmol). After 3 h at rt the reaction mixture was quenched with the addition of 10 mL of 1 M NaOH. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (30% EtOAc/70% hexanes) to provide 2,3-dimethyl-3-(prop-2-en-1-yl)-3*H*-indole (**8**) as a yellow oil (82.0 mg, 74%). TLC R_f = 0.11 (10% EtOAc/90% hexanes). IR (neat): 3079, 3009, 2966, 2827, 2869, 1579 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.0 Hz, 1 H), 7.33–7.21 (m, 2 H), 7.19 (td, *J* = 7.2, 0.8 Hz, 1 H), 5.21–5.11 (m, 1 H), 4.98–4.85 (m, 2 H), 2.66–2.60 (m, 1 H), 2.42 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.26 (s, 3 H), 1.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.6, 154.2, 143.4, 132.5, 127.7, 125.0, 121.8, 119.8, 118.0, 57.5, 41.2, 21.8, 15.9. This compound has been reported previously.[8f]