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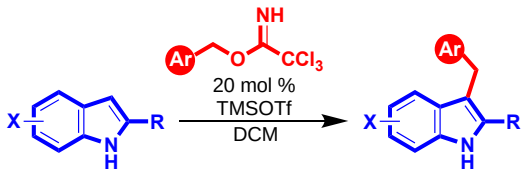

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Friedel-Crafts Alkylation of Indoles with Trichloroacetimidates.

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ABSTRACT

Substituted indole scaffolds are often utilized in medicinal chemistry as they regularly possess significant pharmacological activity. Therefore the development of simple, inexpensive and efficient methods for alkylating the indole heterocycle continues to be an active research area. Reported are reactions of trichloroacetimidate electrophiles and indoles to address the challenges of accessing alkyl decorated indole structures. These alkylations perform best when either the indole or the imidate is functionalized with electron withdrawing groups to avoid polyalkylation.

Indole-based structures have found uses in many enterprises supported by organic chemistry,[1] having an especially large impact on medicinal chemistry.[2] Indoles substituted with benzyl groups at the C3 position are an especially common pharmacophore, being found in many pharmacologically active systems. These systems include anti-tuberculosis agents like **1**,[3] anti-hyperglycemic compounds like **2**,[4] along with antitumor compounds like the autotaxin inhibitor **3**[5] and the topoisomerase inhibitor **4**[6] (Figure 1). Additionally, medicinal chemistry studies in our laboratory have led to the investigation of structures like **5** as potential SHIP phosphatase inhibitors.[7] Clinical success with these structures has also been documented, as demonstrated by the asthma treatment zafirlukast **6.**[8] Owing to their ubiquitous nature, a number of synthetic approaches to the indole ring system have been developed.[9] Attention has now turned to the rapid derivatization and diversification of this heterocycle.[10] Taking advantage of the nucleophilic nature of indole, great strides have been made in the addition of indoles to electron poor alkenes,[10b,11] addition to carbonyls/imines[10b, 10c] and new indole arylation/vinylation reactions.[12] In contrast, functionalization of indoles with sp^3-hybridized electrophiles has received significantly less attention.[10a,13] The direct introduction of alkyl groups to simple indole systems is often problematic, as selectivity problems (C3 vs. *N*-alkylation, mono vs. polyalkylation) are common when alkyl halides are employed with rare exceptions.[14]

Problems with alkyl halides have forced researchers to evaluate alternatives for indole alkylations. Alkylations using activated alcohols with acids can provide alkylated indoles, but these additions require vigorous conditions.[10a,15] Transition metal catalysis has been explored for allylation,[16] benzylation[17] and propargylation[18] of indoles with a number of electrophiles, but these catalysts are expensive, often air-sensitive, and may require an additional Lewis acid additive. Transition metals have also been used to introduce sp^3-hybridized groups to indoles via Heck type reactions[19] or C-H activation,[20] but these methods are limited in terms of the electrophile. While substantial effort has been expended, selective indole alkylation is still often difficult.[21]

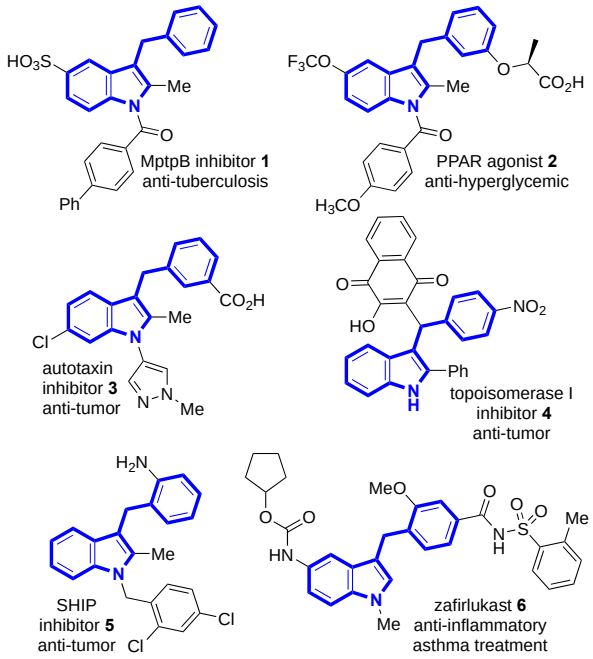


Figure 1. Biologically active 3-benzylindoles.

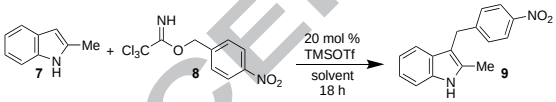
We hypothesized that trichloroacetimidates could provide a useful solution for indole alkylation. Trichloroacetimidates often function as electrophiles in the alkylation of many functional groups including alcohols,[22] carboxylic acids,[23] thiols,[24] anilines,[25] sulfonamides,[26] electron rich alkenes,[27] and

aromatic systems.[28] Trichloroacetimidates provide several advantages over alkyl halides. The imidate possesses a basic nitrogen, which may be activated under mild conditions by a catalytic amount of a Lewis acid. In contrast, stoichiometric base or silver salts are often necessary for the alkylation of indoles with alkyl halides.[8b,8c] Imidate displacement is facilitated by rearrangement of the imidate leaving group to trichloroacetamide, providing an additional thermodynamic driving force for alkylation. This rearrangement facilitates Friedel-Crafts alkylations, requiring only a catalytic amount of a Lewis acid with even electron-poor electrophiles.[28a] Trichloroacetimidates are also easily formed from alcohols and trichloroacetonitrile, and the imidates can be generated *in situ*,[29] providing a method to use inexpensive and readily available alcohols as alkylating agents under mild conditions.

Some alkylation reactions between trichloroacetimidate electrophiles and indoles have been reported.[28d,28f,29-30] Indole itself typically provides C3-alkylation products with trichloroacetimidates.[29b] In cases where C3 is blocked, C2-alkylation usually predominates.[30c] Some aberrant examples have been reported, however, where C2-alkylation could be expected, but instead *N*-alkylation is observed.[30b] This type of alkylation chemistry may be especially useful in the synthesis of libraries of complex indoles for high throughput screening. Before such a library could be constructed, the efficiency, scope and regiochemistry of the indole alkylation must be further defined. Intrigued by the advantages imidates present over alkyl halides, we initiated an investigation to further explore these imidate-based indole alkylations.

Given our interest in substituted indoles like **5** as inhibitors of the 5'-inositol phosphatase SHIP, we began by evaluating 2-methyl indole **7** as the nucleophile (Table 1). The reaction of **7** with 4-nitrobenzyl trichloroacetimidate **8** was investigated, as the nitro group could be reduced to the corresponding amine to provide an interesting tryptamine analog. TMSOTf was utilized as the Lewis acid as this promoter had proven optimal in other studies on the C3-alkylation of 2,3-disubstituted indoles with trichloroacetimidates.[30f]

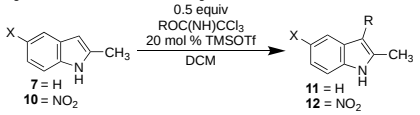
Table 1. Brief optimization of indole alkylation.

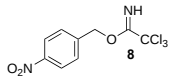
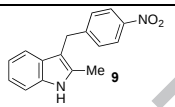
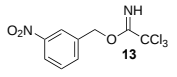
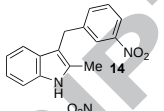
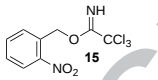
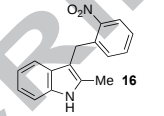
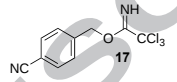
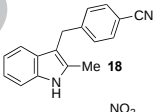
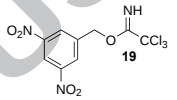
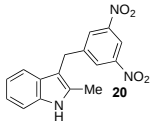
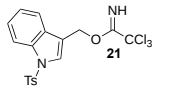
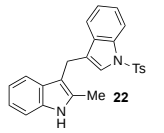
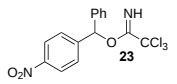
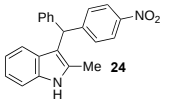
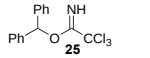
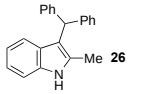
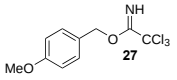
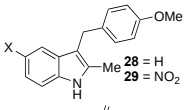
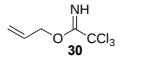
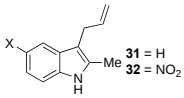
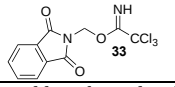
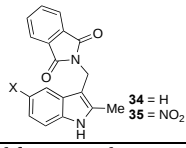


Entry	Solvent	Temp. (˚C)	Equiv. **8**	Yield
1	DCE (0.25 M)	84	0.9	55
2	DCM (0.30 M)	45	0.9	48
3	DCM (0.30 M)	rt	0.9	51
4	DCM (0.10 M)	rt	0.9	41
5	DCE (0.25 M)	84	0.5	59
6	DCM (0.30 M)	rt	0.5	90

Heating the reactants in DCM or DCE gave ~50% yield of the desired benzylated indole product **9**, but isolation of the product was difficult as the alkylation was complicated by indole polyalkylation products. Attempts were then made to lower the reaction temperature to increase selectivity, however this gave an even more complex mixture of products. The amount of imidate electrophile was then lowered, as the starting benzylic alcohols are inexpensive. Use of excess indole provided a significantly more selective process and facilitated separation and isolation of the product. With conditions in hand to effect the selective C3-alkylation of indoles, the scope of the reaction with regards to trichloroacetimidate electrophile was undertaken (Table 2).

Table 2. Alkylation of 2-methylindoles with imidates



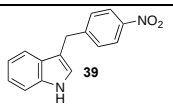
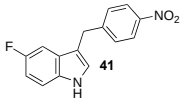
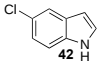
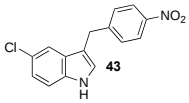
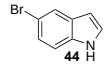
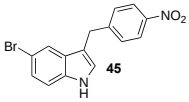
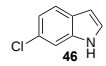
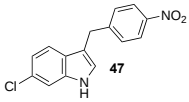
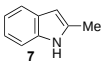
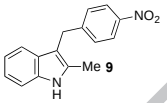
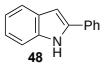
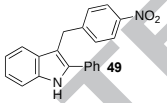
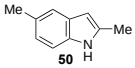
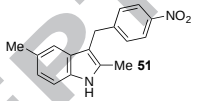
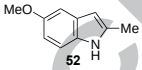
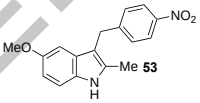
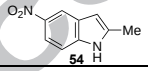
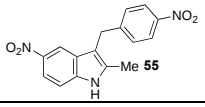
Entry	Indole	Imidate	Product	Yield
1	**7**			90
2	**7**			73
3	**7**			79
4	**7**			73
5	**7**			44
6	**7**			73
7	**7**			60
8	**7**			51
9	**7**			0[a] (**28**)
10	**10**			91 (**29**)
11	**7**			0[a] (**31**)
12	**10**			28 (**32**)
13	**7**			0[a] (**34**)
14	**10**			38 (**35**)

[a]Product could not be isolated from complex mixture.

Both the *m*-nitrobenzyl imidate **13** and the *o*-nitrobenzyl imidate **15** proved to be useful participants, providing the C3-alkylated products in good yield. Other electron poor benzylic imidates also were also successfully employed (entries 4-6). While the isolated yield with the 3,5-dinitrobenzyl imidate **19** was somewhat lower, this was due to difficulties in separating side products, the conversion appeared similar to entries 1-4 by ^{1}H NMR. Secondary imidates were also successfully employed, as shown for indoles **24** and **26**. More reactive 4-methoxybenzyl, allyl and phthalimidomethyl trichloroacetimidates (**27**, **30** and **33**) only gave complex mixtures under these reaction conditions due to polyalkylation of the indole. Attempts to limit side product formation utilizing lower temperatures and/or weaker Lewis acids ($SnCl_2$, $Sc(OTf)_3$) were unsuccessful. We speculated that polyalkylation could be overcome by blocking one of the alkylation sites on C5 of the indole with an electron withdrawing group, and therefore 5-nitro-2-methylindole **10** was also

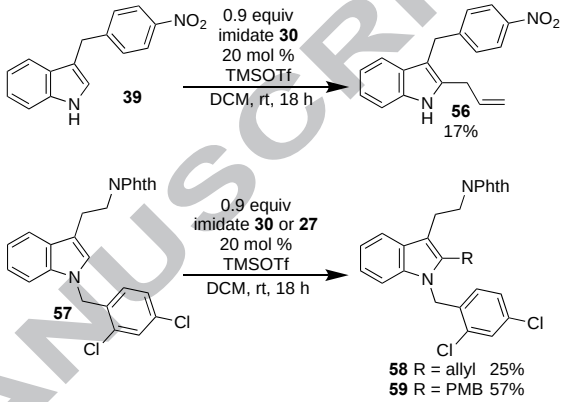
evaluated in alkylation reactions with these imidates. Significantly higher yields were obtained in all three cases when indole **10** was used as a substrate, supporting the hypothesis that the parent indole **7** is too reactive and leads to side products when highly reactive imidates are employed as alkylating reagents. The scope of the reaction with different indole nucleophiles was then explored (Table 3).

Table 3. Alkylation of Different Indoles with 4-Nitrobenzyl trichloroacetimidate

Entry	Indole	Product	Yield
1			72
2			49
3			51
4			45
5			70
6			90
7			83
8			53
9			65
10			82

Unsubstituted indole proved an effective substrate under these conditions, providing a 72% yield of product **39**. Use of indoles halogenated at the 5-position led to lower a slightly lower conversion of ~50% with either a fluorine, chlorine or bromine substituent (entries 2-4). Chlorination at the 6 position of the indole was better tolerated, providing a 70% yield of indole **47**. The influence of a substituent at the C2 position of the indole was also briefly explored, with both a methyl group and a phenyl ring being well tolerated and providing excellent yields of the C3 alkylation product (entries 6 and 7). Some other 2,5-disubstituted indole systems were also evaluated (entries 8-10), and these also provided good yields of the corresponding C3-benzylated indoles.

Analysis of the results in Table 3 indicates a general trend of C2-substituted indoles providing slightly higher yields than with indoles that do not possess a C2 substituent. This may have been due to dialkylation at the C3 and C2 position. To investigate this possibility, indole **39** was reacted with allyl imidate **30**, and while a complex mixture of C and N alkylation isomers was observed a 17% yield or the 2-allyl indole product **56** could be isolated by careful chromatography (Scheme 1). Yields were higher when the indole nitrogen was already alkylated, as in the case of protected tryptamine **57** which underwent successful C2 alkylation with both allyl imidate **30** and PMB imidate **27**. While the yields for these alkylations were modest, this demonstrates a rapid and modular functionalization of an indole core system which may be useful for the preparation of a diverse range of indoles for biological evaluation.



Scheme 1. Alkylation of 3-substituted indoles at C2.

Trichloroacetimidates are excellent alkylating agents for indoles. The reaction proceeds best when an excess of the indole nucleophile is utilized to avoid overalkylation products. This method is especially useful for the preparation of different C3-benzyl indoles, which can be rapidly generated and evaluated for their biological activity. Further studies showed that in some cases C2-alkylation is also possible. This work may find applications in medicinal chemistry studies on alkylated indoles, which have been shown to be pharmacologically relevant scaffolds.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at (*insert web address*). This material includes detailed experimental procedures and NMR data (^{1}H and ^{13}C spectra).

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Highlights

• Indoles may be alkylated by trichloroacetimidates with Lewis acids

• Benzylic and allylic imidates are most effective

• Electron poor imidates and/or indoles perform best as polyalkylation is lower