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Regioselective *N*- and C2-electrophilic substitution of 3-substituted indoles

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Abstract—The reaction of 3-substituted indoles with 2-cyclohexenone under Lewis acid mediated conditions with $Bi(NO_3)_3{\cdot}5H_2O$ has been investigated. We have demonstrated that electrophilic substitution of 3-substituted indoles with 2-cyclohexenone will readily occur at the nitrogen. Furthermore, the extent of regioselectivity is dependent on reaction solvent and the C3-substituent. Excellent conversion is obtained with good to excellent isolated yields of *N*- and C2-adducts. In general, more polar, aprotic solvents (CH_3CN) give greater *N*-selectivity whereas with polar protic solvents (CH_3OH) an increase in the C2-adduct is observed.

Indoles and substituted indoles have attracted considerable attention from both synthetic and medicinal chemists due to their biological activity, for example, the indole alkaloids[1–3] such as harmicine[4–6] and tryptophan,[7] and for their therapeutic use covering a wide range of medicinal purposes.[8] As part of our ongoing medicinal chemistry research programs, the electrophilic substitution of 3-substituted indoles by cyclic α,β-unsaturated ketones has been of particular interest to us. More specifically, we are interested in the development of mild, efficient and robust methodologies for constructing scaffolds that incorporate a diverse array of side arms, containing aromatic nitrogen moieties such as indoles, imidazoles and substituted anilines. Furthermore, this presents an opportunity for the development of new synthetic methods to facilitate electrophilic substitution reactions, which circumvent the undesirable rearrangements and polymerisations that readily occur with indoles under the strongly acidic and basic conditions[1,9] typically utilised. Many groups have employed Lewis acid catalysts to avoid undesirable rearrangements in electrophilic substitution reactions with indoles, such as $InBr_3$,[10] $BF_3{\cdot}Et_2O$,[11] ceric ammonium nitrate (CAN)[12] and $Yb(OTf)_3{\cdot}3H_2O$.[13,14] Recently, bismuth(III) based Lewis acid catalysts have attracted attention. Bismuth(III) compounds are inexpensive, readily available, mild and environmentally friendly catalysts, and have been utilised in an increasingly diverse array of reactions in the form of $BiCl_3$,[15–19] $Bi(OTf)_3$,[20–22] and $Bi(NO_3)_3{\cdot}5(H_2O)$.[23] The range of reactions in which bismuth has been employed is partly due to its high substrate tolerance and ability to react under myriad conditions, thus it is highly likely that the number of practical bismuth(III)-mediated reactions will expand rapidly.[24,25] We have investigated the utility of bismuth(III) nitrate in the addition of cyclohex-2-enone to 3-substituted indoles to synthesise the corresponding *N*- and C2-substituted indoles. Herein we report our preliminary findings on key factors that affect the *N*/C2 adduct ratios.

Pivotal to our interest in this area was the recent report of specific C2 addition of α,β-unsaturated ketones to substituted 3-methylindoles by Srivastava and Banik.[23] This report indicated a facile route to C2 addition products in moderate to good yields (45–85%). Suitably encouraged by this method, we commenced our investigations using 3-methylindole and cyclohex-2-enone in CH_2Cl_2. Somewhat surprisingly we observed differences in the reaction outcome, viz. 28% yield versus a reported 55%[23] isolated yield of the desired C2 analogue. Moreover, we successfully isolated the *N*-adduct (7% yield) (Scheme 1). Analysis of the NMR spectra of both products revealed considerable differences making them readily distinguishable from each other,[26] regardless of the substituent at C3. In the ^1H NMR spectra these are:

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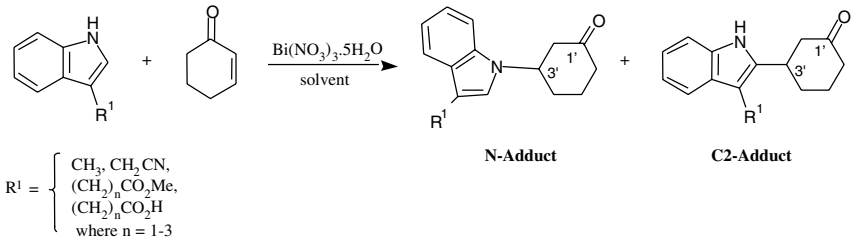


Scheme 1.

- *N*-adduct $\delta \sim 4.5$ (H3′) and C2-adduct $\delta \sim 3.3$ (H3′). These differences are comparable with the changes in the methyl chemical shift noted in *N*-methyl and C2-methyl indoles. Analogous differences were also noted in the ^{13}C NMR spectra:
- *N*-adduct C3′ ~54 ppm; C2-adduct C3′ ~36 ppm.
- *N*-adduct 208 ppm (C1′); C2-adduct 211 ppm (C1′).

Intrigued by the ease of entry into the *N*-alkylated adducts, given that such adducts are typically the result of addition under basic conditions[9] and by our desire to further understand the impact of $Bi(NO_3)_3{\cdot}5H_2O$ in determining the product yield and ratios, we chose to examine this reaction further. In addition, we could foresee a considerable advantage in generating both C2- and *N*-alkylated adducts, if we were able to control (and predict) the reaction outcome. Accordingly, we examined the electrophilic substitution of a range of 3-substituted indoles by cyclohex-2-enone under Lewis acid catalysis ($Bi(NO_3)_3{\cdot}5H_2O$) with particular attention being paid to the effect of both the C3-substituent and reaction solvent. The results of these reactions are given in Table 1.

In a typical reaction[27] cyclohex-2-enone (1 mmol) and a 3-substituted indole (1 mmol) were stirred in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ (0.25 mmol) in either aprotic (CH_2Cl_2), polar and aprotic (CH_3CN) or protic (CH_3OH) solvents (2 mL).

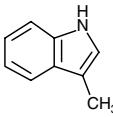
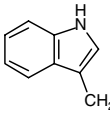
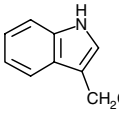
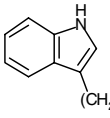
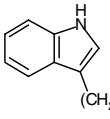
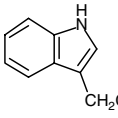
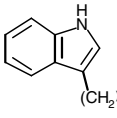
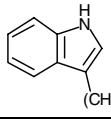
Table 1 highlights the *N*-adduct as the favoured product (entries 6–12, 14, 17 and 20–22). It is also apparent that CH_2Cl_2 is a poor solvent for these reactions affording highly variable yields from excellent (entries 1, 10 and 22) to poor (entries 4, 7, 13, 16 and 19) suggesting poor synthetic utility. With respect to the *N*-selectivity there are a number of trends. *N*-adducts are formed very readily as the major adduct in CH_3CN whereas formation of C2 adducts appears to be favoured by a polar protic solvent (CH_3OH) (entries 3, 15 and 24). In the case of 3-methylindole both CH_3CN and CH_3OH as reaction solvents afforded C2 addition (entries 2 and 3, respectively), with the latter case yielding exclusively the C2 adduct. As the 3-substituent becomes more complex it exerts considerable effects on selectivity and reactivity. For $–CH_2CN$ no reaction was observed in either CH_2Cl_2 or CH_3CN (entries 4 and 5, respectively) and reaction was only observed in CH_3OH in conjunction with a substantial reduction in reaction rate (89 h). However it does afford solely the *N*-adduct (entry 6).

Chain elongation and the introduction of an ester moiety (<4 carbons) favours *N*-addition in CH_3CN and CH_3OH. It is noteworthy that in CH_3OH as the chain extends there was a corresponding reduction in the amount of *N*-adduct observed (entry 9 ($–CH_2CO_2CH_3$)*N*:C2 = 2.7:1; entry 12 ($–CH_2CH_2CO_2CH_3$)*N*:C2 = 1.3:1) with the crossover point to C2 dominance after installation of the methyl butyrate (entry 15 ($–CH_2CH_2CH_2CO_2CH_3$)*N*:C2 = 1:2). The corresponding reactions with free carboxylic acids produced essentially the same trend, now observed in both CH_3CN and CH_3OH. The crossover from *N* to C2 selectivity occurred at the same point (entries 23 and 24), but significantly greater quantities of the C2 adduct are generated. This is highly suggestive of the substituent influencing the reaction outcome, most likely via Lewis acid–substrate complexation. The lower yields of C2-adduct in the case of methyl esters suggests that the interaction with $Bi(NO_3)_3{\cdot}5H_2O$ which promotes C2-adduct formation is favoured with the free acid.

It is also known that bismuth compounds can interact with carboxylic acid moieties[28] and this interaction was especially evident in CH_3OH with the formation of the methyl esters (entries 18, 21 and 24). The isolation of the methyl esters suggests that bismuth complexed to the carboxylic acid, thus catalysing methyl ester formation. ^{13}C NMR studies were conducted to observe the interaction of the carboxylic acid carbonyl[29] with $Bi(NO_3)_3{\cdot}5H_2O$ in CH_3OH-d_4. After 1 h it was apparent that significant complexation had taken place with the loss of the carboxyl carbonyl signal at 177 ppm and the appearance of a signal at 179 ppm, presumably due to complexation with Bi^{3+}. As the reaction progressed, formation of the methyl ester was apparent with a carbonyl signal appearing at 175 ppm. After 24 h all of the carboxylic acid had been converted to the methyl ester. This observed interaction of Bi^{3+} with the carboxylic acid moiety in conjunction with the contrast in selectivities for the methyl esters and the corresponding acids suggests that varying degrees of Lewis acid–substrate complexation is taking place which in turn influences the regioselective outcome substantially.

In summary, we have demonstrated that the regioselective *N*- and C2-electrophilic substitution of 3-substituted indoles by cyclohex-2-enone with $Bi(NO_3)_3{\cdot}5H_2O$ as the Lewis acid is dependent upon reaction solvent and the C3-substituent. In particular, the polar aprotic solvent (CH_3CN) facilitates selective formation of *N*-adducts very readily. As the solvent becomes protic (CH_3OH) an increase in formation of the C2-adduct is observed, but in general a tendency towards selective *N*-substitution is maintained. In addition, as the as chain length

Table 1. *N*- and C2-adducts formed in the $Bi(NO_3)_3{\cdot}5H_2O$ mediated electrophilic substitution of 3-substituted indoles with 2-cyclohexen-1-one

Entry	3-Substituted indole	Solvent	Adduct ratios[a]		Conversion by NMR (%)[b]	Isolated yield[c] (%)
			N	C2		
1		CH_2Cl_2	1	1	100	99
2		CH_3CN	1	1.3	100	100
3		CH_3OH	—	C2-only	100	100
4		CH_2Cl_2	NR	NR	—	—
5		CH_3CN	NR	NR	—	—
6		CH_3OH	*N*-only[d]	—	80	74
7		CH_2Cl_2	NR	NR	—	—
8		CH_3CN	4	1	100	92
9		CH_3OH	2.7	1	100	76
10		CH_2Cl_2	3	1	96	92
11		CH_3CN	*N*-only	—	93	70
12		CH_3OH	1.3	1	100	87
13		CH_2Cl_2	NR	NR	—	—
14		CH_3CN	*N*-only		73	81
15		CH_3OH	1	2	100	85
16		CH_2Cl_2	NR	NR	—	—
17		CH_3CN	4	1	92	90
18		CH_3OH	1[e]	1[e]	100	93
19		CH_2Cl_2	NR	NR	—	—
20		CH_3CN	*N*-only	—	96	92
21		CH_3OH	3[e]	1[e]	100	97
22		CH_2Cl_2	*N*-only	—	100	71
23		CH_3CN	1	3	100	86
24		CH_3OH	1[e]	6[e]	100	59

Reactions were conducted in either duplicate or triplicate.
[a] NR = No reaction.
[b] 18 h, rt (25–30 °C) based on consumption of cyclohex-2-enone
[c] Combined yield (*N*- and C2-adducts).
[d] 89 h.
[e] Isolated as the corresponding methyl esters.

increases to four carbons (butyric acid) we see a preference for the formation of C2-adduct in CH_3OH (a polar, protic solvent).

We are currently utilising this method to develop a diverse library of *N*- and C2-adducts of C3-substituted indoles relevant to our medicinal chemistry program and will report our findings in due course.

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26. Representative data:
Methyl 1-(3-oxocyclohexyl)indole-3-ethanoate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69–1.83 (1H, m), 2.06–2.56 (5H, m), 2.74–2.94 (2H, m), 3.72 (3H, s, CO_2CH_3), 3.79 (2H, s, $CH_2CO_2CH_3$), 4.63 (1H, tt, J = 10.7, 4.1 Hz), 7.13–7.27 (3H, m), 7.33 (1H, d, J = 8.2 Hz), 7.63 (1H, d, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2 (CH_2), 31.0 (CH_2), 31.4 (CH_2), 40.7 (CH_2), 48.1 (CH_2), 51.8 (CO_2CH_3), 54.0 (CH), 108.1 (C), 109.2 (CH), 119.2 (CH), 119.7 (CH), 122.0 (CH), 122.5 (CH), 127.7 (C), 135.5 (C), 172.2 (CO_2CH_3), 207.9 (C=O). EI *m/z* (%) 285 (47%, M^+), 226 (73, M^+-OCH_3), 156 (11), 130 (100), 69 (11), 41 (16). HRMS (EI) *m/z* calcd for M^+, $C_{17}H_{19}NO_3$: 285.1360. Found: 285.1369.
Methyl 2-(3-oxocyclohexyl)indole-3-ethanoate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78–2.00 (2H, m), 2.16 (2H, br d, J = 10.2 Hz), 2.34–2.45 (1H, m), 2.50–2.57 (1H, m), 2.59 (1H, d, J = 11.9 Hz), 2.69 (1H, dd, J = 14.1 Hz, 5.0 Hz), 3.45 (1H, tt, J = 11.2 Hz, 4.0 Hz), 3.67 (3H, s, CO_2CH_3), 3.72 (2H, s, $CH_2CO_2CH_3$), 7.12–7.19 (2H, m), 7.31 (1H, d, J = 7.8 Hz), 7.57 (1H, d, J = 7.9 Hz), 8.03 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3 (CH_2), 30.1 (CH_2), 31.3 (CH_2), 36.3 (CH), 41.3 (CH_2), 47.2 (CH_2), 52.0 (CO_2CH_3), 104.1 (C), 110.7 (CH), 118.6 (CH), 120.0 (CH),122.0 (CH), 128.2 (C), 135.2 (C), 137.8 (C), 172.1 ($\underline{C}O_2CH_3$), 210.0 (C=O). EI *m/z* (%) 285 (51%, M^+), 226 (38, M^+-OCH_3), 212 (100), 184 (29), 168 (42), 156 (53), 130 (64), 95 (33). HRMS (EI) m/z calcd for M^+, $C_{17}H_{19}NO_3$: 285.1360. Found: 285.1361.
27. General experimental procedure: The solvent (DCM, CH_3CN or MeOH, 1 mL per 100 mg of substrate) was added to the indole (200 mg) and the mixture was stirred. $Bi(NO_3)_3{\cdot}5H_2O$ (0.2 equiv) was added followed immediately by the addition of cyclohexenone (1 equiv). The reaction mixture was stirred at room temperature overnight (approximately 18 h). CH_2Cl_2 was added to the reaction mixture and the mixture was filtered. If the product was not a carboxylic acid, the organic layer was washed with $NaHCO_3$ saturated solution, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the C2- and *N*-adducts. In the case of the carboxylic acids, the organic layer was washed with $NaHCO_3$ satd. solution. The aqueous phase was made acidic with aqueous HCl (1 M) and extracted with EtOAc (3×). The combined EtOAc layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the desired products. All spectral data were consistent with the structures indicated. HRMS were conducted at the University of Wollongong, Biomolecular Mass Spectrometry Laboratory, NSW, Australia.
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29. Acetic, propanoic and butyric acid side chains were examined. The reported chemical shifts are associated with 3-indolebutyric acid and formation of its methyl ester.