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PAPER

Study of N^1-alkylation of indoles from the reaction of 2(or 3)-aminoindole-3-(or 2)carbonitriles with DMF-dialkylacetals†

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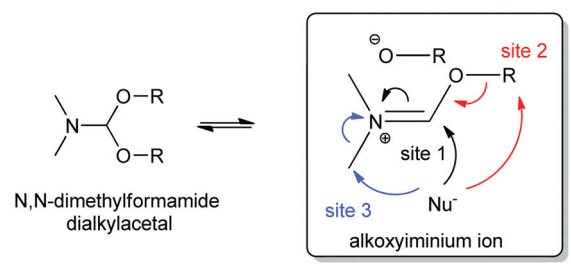
The condensation of 2-aminoindole-3-carbonitriles and their 3-aminoindole-2-carbonitrile isomers with various DMF-dialkoxyacetals was investigated under microwaves. The appearance of reactive and versatile alkoxyiminium species allowed convenient access to indole precursors of building blocks with potential biological activity. The experimental results have been rationalised using DFT calculations of theoretical descriptors based on the electrostatic potential.

Introduction

Formamide acetals, also called *N*,*N*-dimethylformamide dialkylacetals, are versatile compounds with an important role in organic synthesis.[1] These reagents are able to perform two categories of chemical reactions, namely formylation and alkylation.[1] For the latter, formamide acetals have been used in the synthesis of esters from acids[2] and amides,[3] the synthesis of ethers or thioethers from phenols[4] and heterocyclic thiols,[5] or the alkylation of intracyclic amines in indoles and benzimidazoles.[6] As formylating agents, *N*,*N*-dimethylformamide dialkylacetals are mainly used for the formation of enamines from active methylene groups to yield *N*,*N*-dimethylenamines.[7] They can also be condensed with amines or amides to form formamidines.[8] All of these intermediates are found to be very useful in the formation and modification of many types of heterocyclic compounds. In particular, *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA, **1a**) was used as a building block in heterocyclic synthesis.[7–9] Its ability to participate in formylation or alkylation reactions was attributed to the generation of an alkoxyiminium ion as depicted in Scheme 1.

According to various authors,[4–9] heating the reaction mixture would be beneficial to the presence of the ionic species by helping to eliminate the alkoxide counterpart. Recent work by Priefer and his group on the methylation of phenols[4] has confirmed that microwave irradiation of the reaction mixture had a favorable effect, although the reader should be aware that they worked in pressurized vials (it is known that the combination of pressure and heating enhances the thermal effect[10]). At the same time, Threadgill and his group studied the synthesis of quinazolin-4-ones *via* formylation of the starting anthranilamides with sterically unhindered formamide acetals.[11] This cyclocondensation was followed by alkylation of the N^3-nitrogen atom of the quinazolin-4-one. The most important novelty of the work described by this group is that, for the first time, evidence was found of the existence of a third electrophilic site present on the hindered alkoxyiminium species (site 3 in Scheme 1). Attack at this site has been shown to be driven by the size of the



Scheme 1 General formula of *N*,*N*-dimetylformamide dialkylacetals and their alkoxyiminium ion. On the right, the frequently described electrophilic sites (site 1 and site 2) and the recently suggested third site (site 3) are indicated.[11]

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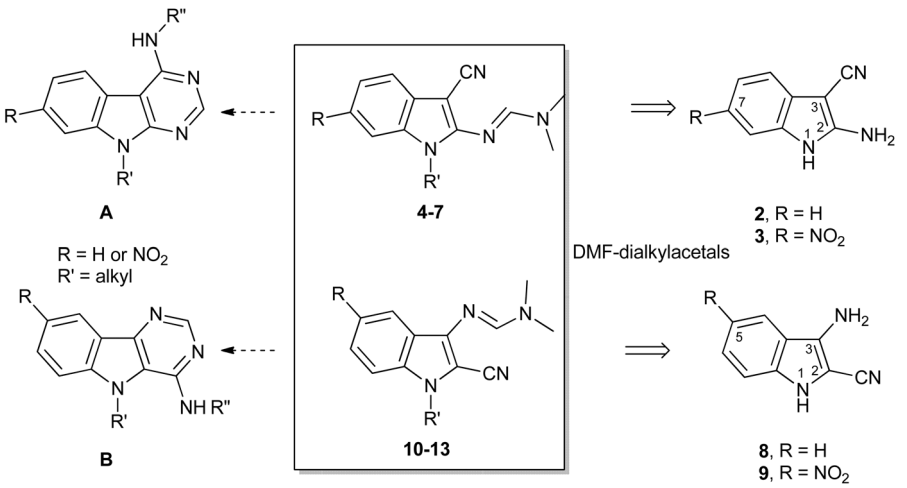


Scheme 2 Envisioned synthesis of the target *N*,*N*-dimethylformimidamides **4** (R and R′ = H) and **5** (R = H and R′ = alkyl) from 2-aminoindole-3-carbonitrile (**2**);[13] **6** (R = NO_2 and R′ = H) and **7** (R = NO_2 and R′ = alkyl) from **3**[13] and their 3-aminoindole-2-carbonitrile isomers: **10** and **11** from **8**;[14] **12** and **13** from **9**.[14]

O-alkyloxyacetal group (*e.g.* isopropoxy or tertiobutoxy groups). The heating mode used in the work was traditional (oil bath) and the reaction times were very long (16–24 h) before significant results were obtained.

These recent results prompted us to publish our own work started one year ago on the use of DMF-dialkylacetals either as a source of electrophilic one-carbon units or as an alkylating agent of various *N*,*N*-dimethylformimidamide derivatives (**4**, **5**, **6** and **7** in Scheme 2) which can be used as key precursors to a wide range of tricyclic pyrimido[5,4-*b*]indoles (see **A** in Scheme 2) from the appropriate 2-aminoindole-3-carbonitriles (**2** and **3**). The study was also extended to the novel 2-amino-indole-3-carbonitrile isomers (**8** and **9**) to study the influence of the amine nucleophilicity on the reaction result for the further synthesis of various pyrimido[4,5-*b*]indole homologues (B in Scheme 2). This work also relates to our overall approach which consists of studying the utility of microwaves in heterocyclic chemistry.

In order to rationalise the experimental trends observed in terms of reactivity of the various electrophilic intermediates (alkoxyiminium ions) formed, quantum chemistry calculations have been performed using density functional theory (DFT). The analysis of computed theoretical descriptors based on the electrostatic potential provides useful qualitative insights into the behaviour of the alkoxyiminium ions according to their chemical structure.

Results and discussion

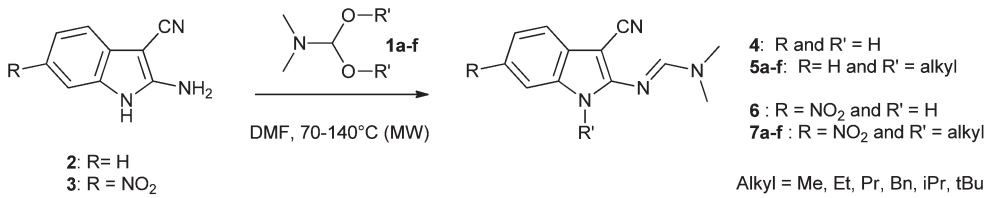
Synthesis—experimental observations of reactivity

The main part of our work involves the study of the reaction of various aromatic cyanoenamines (**2** and **3** or **8** and **9**) with DMF-dialkylacetals (**1a–f**) to yield *N*,*N*-dimethylformimidamides (**4–7** and or **10–13**), which are potent key precursors of 6,5,6-tricyclic homologues of the basic 4-aminoquinazoline. Such a pharmacophore is present in a wide range of novel ATP-competitive inhibitors of kinases that have received approval for the treatment of cancer (series **A** and **B** in Scheme 2).[12] A literature survey revealed that this strategy was described for the synthesis of 4-anilinoquinazolines[8] but was never described in the case of pyrimido[5,4-*b*]indoles (**A**) and pyrimido[4,5-*b*]-indole derivatives (**B**).

In the current work, the main part of our studies have been conducted from 2-aminoindole-3-carbonitriles (**2** and **3**) precursors.[13] These cyanoenamines were heated with the usual commercially available DMF-dialkylacetal derivatives that possess unhindered (**1a–d**) or bulky groups (**1e–f**). The general method for the synthesis of *N*′-alkylated formimidamides (**5** and **7**) consisted of microwave irradiation (800 W) of a mixture of 2-aminoindole-3-carbonitrile (**2** or **3**) and DMF-dialkylacetals (**1a–f**) in dimethylformamide (DMF) at atmospheric pressure (Scheme 3). For each starting DMF-dialkylacetal derivative (**1a–f**), the temperature of the reaction inside the vessel and the average time of exposure to microwaves were optimized. The reaction parameters of this thermally-dependent reaction can be strictly controlled by the use of microwave reactors especially designed for organic synthesis, allowing convenient access to various formimidamide precursors (**4**, **5**, **6** and **7**). The results of these investigations, reported in Table 1, confirmed that formylation and alkylation of the starting 2-aminoindole-3-carbonitriles (**2** and **3**) can be obtained in the same experiment, leading to the target *N*,*N*-dimethylformimidamides (**5a–f** and **7a–f**). The reaction occurred in convenient temperature and time conditions; in comparison with the traditional heating mode (an oil bath in our case), the time of the reaction was decreased considerably from about 24 h to only 2 h for the longest cases. The yields obtained are acceptable for a cascade reaction, except in the case of the bulky *O*-alkyloxy groups (*e.g.* **1e** and **1f**) for which a N^1-methylated by-product (**4** and **6**) appeared respectively from **2** and **3**.

This result suggested the possibility of an unexpected attack of the intra-cyclic amine on the sp^3-C of the methyl group of the starting DMF-dialkyloxyacetal which seemed more stabilized in its alkoxyiminium ion form. It is worth noting that the procedure was convenient and had an easy work-up.

Because it can be expected that the position of the amino group on the indole ring (2 or 3) can influence its nucleophilicity, we extended the reaction to the two regioisomers (**8** and



Scheme 3 Synthesis of formimidamide derivatives **4** and **5a–f** (from **2**) or **6** and **7a–f** (from **3**): for reaction times and yields see Table 1.

Table 1 Synthesis of formimidamide derivatives **4–5** or **6–7** from **2** or **3**[a]

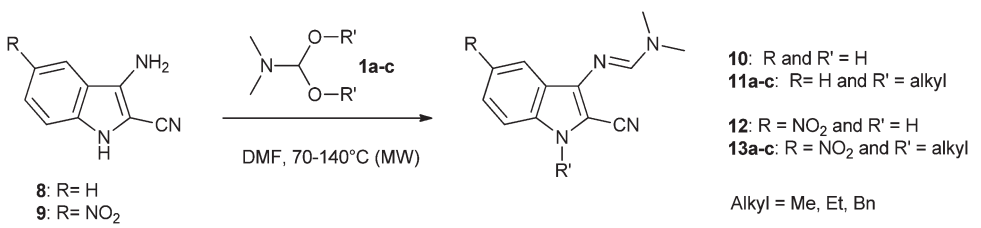
Starting indole	DMF-dialkyacetal (R′)	Temperature (°C)	Time (min)	Product (R′)	Yield[b](%)
2	**1a** (Me)	90	15	**4** (H)	57
2	**1a** (Me)	120	45	**5a** (Me)	66
2	**1b** (Et)	120	50	**5b** (Et)	66
2	**1c** (Bn)	120	30	**5c** (Bn)	65
2	**1d** (Pr)	120	30	**5d** (Pr)	69
2	**1e** (iPr)	120	30	**5e** (iPr)	35[c]
2	**1f** (*t*Bu)	120	30	**5f** (*t*Bu)	49[d]
3	**1a** (Me)	70	4	**6** (H)	67
3	**1a** (Me)	90	30	**7a** (Me)	55
3	**1b** (Et)	120	60	**7b** (Et)	75
3	**1c** (Bn)	120	30	**7c** (Bn)	60
3	**1d** (Pr)	120	30	**7d** (Pr)	72
3	**1e** (iPr)	120	30	**7e**(*i*Pr)	39[c]
3	**1f** (*t*Bu)	120	30	**7f** (*t*Bu)	13[d]

[a] Reactions were performed on a mmol scale from **2** or **3** with 10 equiv. of DMF-dialkylacetal (**1a–f**), at atmospheric pressure under microwaves (MW) at 800 W (RotoSYNTH™ from Milestone S.r.l., Italy). [b] Yield of isolated product (column chromatography using dichloromethane–petroleum ether; 5 : 5, v/v). [c] In these experiments 18% of **5a** and 34% of **7a** were isolated from **2** and **3** respectively. [d] In these experiments 19% of **5a** and 55% of **7a** were isolated from **2** and **3** respectively.

9)[14] of the preceding indoles (**2** and **3**). Our investigation was limited to smaller groups of DMF-dialkyloxyacetals for which the expected products would be more reliably obtained (Scheme 4 and Table 2).

It is important to note that the positions of the amine and cyano groups do not significantly influence the final result, although one can observe that the reaction seemed slightly more favorable when the amine was in position 3 of the starting indole (*e.g.* **8** and **9**). The products (**4–7** or **10–13**) were rapidly obtained in most cases, and with good yields. The position of the nitro group (which is *para* or *meta* to the indole nitrogen N^1-atom, see **3** and **9** respectively) accelerated the reaction by an important electron-withdrawing effect, compared to unsubstituted indoles (**2** and **8**). This effect was particularly strong in the case of 5-nitro-3-aminoindole-2-carbonitrile (**9**), from which product (**12**) was never obtained using DMF-DMA (**1a**). The synthesis of the N^1-free compound (**12**) was possible with the use of other DMF-dialkyloxyacetals, like DMF-DEA (**1b**) or DMF-dibenzylacetal (**1c**), and by strict control of the reaction time in order to stop the synthesis at the formimidamide state (**12**).

At this stage of our work, some comments can be made concerning the microwave procedure as well as the mechanism of the reaction (Scheme 4). Concerning the technical aspect, the choice of a reactor able to work at atmospheric pressure was guided by our previous experience in the use of microwaves in heterocyclic synthesis, especially in the chemistry of quinazolines.[15] The open vessel microwave experiments have some advantages, such as the possibility of easier scale-up and the use of usual laboratory glassware. Our choice was also influenced by a recent work describing the tendency of pressure to accumulate when DMF-DMA was heated in pressurized vials, especially under microwaves.[4] Reactions were performed between 70 °C and 140 °C, and irradiation at 800 W was sufficient to efficiently reach the programmed temperature. This parameter was monitored *via* a contactless-infrared pyrometer, which was calibrated by control experiments with a fibre-optic contact thermometer. It should be noted that the non-alkylated products (**4**, **6**, **10** and **12**) were obtained in shorter times and at lower temperatures (except for **13a**) than their N^1-substituted analogues (compounds **a–f** in the four series: **5**, **7**, **11** and **13**). This demonstrates that the first reaction to occur in the reactor is the nucleophilic attack of the aromatic amine on the electrophilic site of the DMF-dialkylacetal derivative leading to the N^1-free *N*,*N*-dimethylformimidamides (**4** and **6** from **2** and **3**) or (**10** and **12** from **8** and **9**) as depicted in Schemes 3 and 4. Completion of the reaction to the alkylated intra-cyclic nitrogen atoms was obtained after an increase of the temperature and with longer irradiation times. We confirmed that the alkyl groups introduced at N^1 of the starting indoles were from the *O*-alkyl groups of the starting DMF derivatives (attack on site 2 in Scheme 4) and not from the *N*-methyl substituents, except in the case of the di-isopropyloxy and di-*t*-butyloxy DMF



Scheme 4 Synthesis of formimidamide derivatives **10** and **11a–c** (from **8**) or **12** and **13a–c** (from **9**): for reaction times and yields see Table 2.

derivatives (respectively **1e** and **1f**) for which significant amounts of N^1-methylated products (**5a** or **7a**) were obtained (attack on site 3 in Scheme 4).

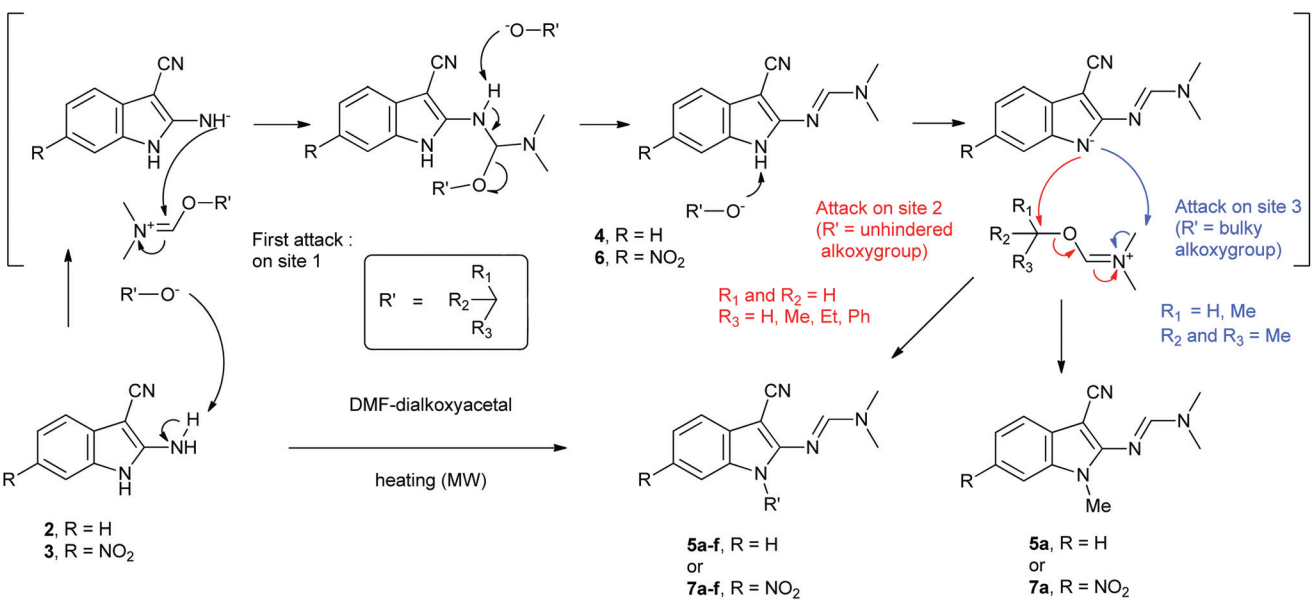
It may be suggested that the fast enhancement of the temperature and strict control of the parameters inside the microwave reactor will favor generation of the alkoxyiminium ion by helping to eliminate its alkoxide counterpart. This phenomenon was particularly favoured in the case of bulky alkyl groups (*e.g.* **1e** and **1f**) where electron-donor effects stabilized the iminium form and then resulted in *N*-methylation of the intra-cyclic nitrogen by attack on site 3 (Scheme 5), in competition with its attack on the hindered electrophilic site (site 2 in Scheme 1). As explained in the introduction, this electrophilic *N*-methylation of compounds was recently described by Threadgill and his group[11] in a study on the synthesis of quinazolin-4-ones by reaction of anthranilamides with DMF-dialkylacetals after traditional heating for long periods (15–24 h). These authors concluded that DMF-dialkylacetals can thermally eliminate one alkoxide to generate a cationic species that can act as an electrophile at two sites. In our case, the very rapid and efficient heating of the reactions was due to the favorable dielectric properties of the reaction mixture. The solvent used in our process, DMF, possesses a tan δ (loss dissipation factor[16]) value high enough to guarantee an efficient heating under microwaves at the frequency of 2450 MHz. For their part, DMF-dialkylacetals heated well under microwaves and the combination of this reactant and solvent was in favor of fast and efficient heating. In the conditions described in our study, we were not able to observe *N*-methylated derivatives (*e.g.* **5a** and **7a**) in the case of *O*-Et (**1b**), *O*-Bn (**1c**) and *O*-Pr (**1d**) derivatives. A suggestion that the ionic alkoxyiminium species was favoured by exposure to the microwaves is not realistic in the present case, since the results observed in traditional heating conditions by Threadgill[11] demonstrated that these cationic species are the consequence of a simple thermal effect. Therefore, their formation can be vigorously accelerated under microwave irradiation, as is the case for many thermally controlled organic reactions.

The presence of the alkoxyiminium species can explain the result observed in the case of the bulky di-isopropyloxy, di-*t*-butyloxy acetals (**1e** and **1f**), for which longer reaction times or increased reaction temperatures were needed. At this stage of the mechanism the intra-cyclic nitrogen atom has the choice between nucleophilic attack on the alkoxy sp^3-carbon (site 2 in Scheme 1) or on the *N*-methyl sp^3-carbon (Site 3 in Scheme 1). The final result was the consequence of the steric access to these two partners. It constitutes a further example of the existence of a third electrophilic site on the alkoxyiminium species formed from hindered DMF-dialkyloxyacetals. Having considered the above, the purpose of this work is also to alert readers to the possibility to observe varying and interesting phenomena when

Table 2 Synthesis of formimidamide derivatives **10–11** or **12–13** from **8** or **9**[a]

Starting indole	DMF-dialkyacetal (R′)	Temperature (°C)	Time (min)	Product (R′)	Yield[b] (%)
8	**1a** (Me)	90	15	**10** (H)	43
8	**1a** (Me)	90	30	**11a** (Me)	77
8	**1b** (Et)	140	60	**11b** (Et)	72
8	**1c** (Bn)	140	60	**11c** (Bn)	65
9	**1b** (Et)	90	10	**12** (H)	63
9	**1a** (Me)	70	2	**13a** (Me)	77
9	**1b** (Et)	120	30	**13b** (Et)	86
9	**1c** (Bn)	120	30	**13c** (Bn)	95

[a] Reactions were performed at atmospheric pressure on a mmol scale from **8** or **9** with 10 equiv. of DMF-dialkylacetal (**1a–f**), under microwaves (MW) at 800 W (RotoSYNTH™ from Milestone S.r.l., Italy). [b] Yield of isolated product (column chromatography using dichloromethane–petroleum ether; 5 : 5, v/v).



Scheme 5 Proposed mechanism for the formation of the N^1-methylated products (**5a** or **7a**) *via* attack of intra-cyclic N^1 of the indoles (**2** or **3**) on the Me–*N* (sp^3-C) of the alkoxyiminium ion.

this very powerful heating mode is associated with thermally unstable reagents, which can be the source of various key reactants in organic synthesis. Users of these classes of compounds should be aware of the fact that traditional, but sometimes slow, unexpected thermal processes can be dramatically accelerated under microwave irradiation.[17]

Computational study

The strong dependence of charge on the reactivity of the studied molecules has led us to compute quantum chemical descriptors based on the electrostatic potential. Previous studies have demonstrated the applicability of molecular surface electrostatic potential (MEP) minima and maxima for the theoretical assessment of chemical reactivity.[27–30] We have therefore computed the MEP on the molecular cation surfaces, and measured the local maxima values (i) perpendicular to the NCO plane (for C_1) (ii) along the O–C bond (for C_2) and (iii) along the N–C bonds (for C_3 and C_4) of the various carbon atoms that appear as potential electrophilic sites in the alkoxyiminium ions. Electrostatic potentials at the nuclei (EPN) of the carbon atoms (V_C)[18,19] that behave as potential electrophilic sites have also been calculated. The EPN index was first defined by Wilson in 1962.[18] Galabov was the first to use this descriptor as a reactivity index for organic compounds.[20–26] In particular, the EPN index has excellently described a number of charged-controlled reactions.[22–26]

Table 3 presents the MEP (V_S) and EPN (V_C) values of the carbon atoms corresponding to the first, second and third potential sites of nucleophilic attack (see Scheme 6) highlighted from the experimental data. The V_S values reveal interesting trends between the relative reactivity of the various carbon atoms towards nucleophilic agents and the substituent carried by the alkoxy oxygen. Owing to the cationic nature of the iminium ions, the electrostatic potential shows only positive values on the surface. A regular variation is observed in Table 3 as a function of the substituent carried by the alkoxy oxygen atom. Indeed, the branching of this substituent leads to a better distribution of the positive charge over the whole structure, and hence to a global decrease of the electrostatic potential, in the order: Me > Et > *i*-Pr > *t*-Bu. On the other side, the C1 V_S value is always significantly greater than the other carbon atoms and is independent of the substituent carried by the oxygen atom of the alkoxyiminium ion. This trend is in agreement with the C1 preference observed experimentally for nucleophilic attacks. Furthermore, the branching of the substituent on the alkoxy oxygen induces a significant decrease of the electrostatic potential in the C2 region of the molecule. This suggests that the approach of the nucleophilic agent to C2 becomes less and less favoured from the Me to the *t*-Bu substituents. Indeed, as illustrated by the V_S values, C2 is the second electrophilic site in the methoxy derivative, whereas it is only the third in the ethoxy compound and it falls to the fourth position in the *i*-propoxy and *t*-butoxy derivatives. This switching between the C2 and the C3 and C4 sites is in good agreement with the experimental results. It is also worth noticing that the C3 V_S value is always greater than the C4 value, suggesting that the *trans* carbon site (C3) (according to the alkoxy substituent) is always the most electrophilic of the two carbon atoms (site 3 of Scheme 1).

Table 3 MEP (V_S) and EPN (V_C) values computed around the four potential electrophilic sites of the various alkoxyiminium ions (SMD/M06-2X/6-31+G(d,p))

V_S (a.u.)	Me	Et	*i*-Pr	*t*-Bu
C1	0.2097	0.2077	0.2059	0.1986
C2	0.1724	0.1643	0.1550	0.1516
C3	0.1720	0.1696	0.1681	0.1667
C4	0.1600	0.1585	0.1574	0.1550
V_C (a.u.)	Me	Et	*i*-Pr	*t*-Bu
C1	−14.3932	−14.3970	−14.4006	−14.4061
C2	−14.5048	−14.5028	−14.5005	−14.4984
C3	−14.5081	−14.5104	−14.5126	−14.5152
C4	−14.5228	−14.5251	−14.5275	−14.5306

R = Me, Et, *i*-Pr, *t*-Bu

Scheme 6 Chemical structure of the alkoxyiminium ions investigated through the DFT calculations together with the numbering of the carbon atoms relevant for the electrophilic attack.

Considering the EPN index, note at first that V_C values are always negative, and the more positive they are the more "electrophilic" the corresponding atomic sites are. Whatever the substituent carried by the oxygen atom of the alkoxyiminium ion, the following order of electrophilic character is established: C1 > C2 > C3 > C4.

In agreement with the MEP analysis, the C1 site is the most electrophilic carbon atom. Indeed, the C1 V_C value is always significantly greater than the other carbon atoms. Secondly, it is worth noting that the V_C values computed for C2 are greater (more electrophilic) than those computed for C3 and C4. Surprisingly, from Me to *t*-Bu, the values show a relative electrophilicity that increases for C2, whereas it decreases for C3 and C4. This is clearly not in agreement with the experimental results since the C2 atom appears to be the second preferred site of nucleophilic attack of methoxy and ethoxyiminium ions, but not of *i*-propoxy and *t*-butoxyiminium ions. This lack of consistency with the EPN index has already been observed in a theoretical reactivity study of the benzylation reaction.[26] It is in contrast with the agreement obtained using this parameter for other electrophilic or nucleophilic reactions[22–26] and can be rationalized by the influence of the steric hindrance of the C2 carbon atom, not accounted for by V_C, which is significantly enhanced upon substitution at this position. The MEP maps shown in Fig. 1 illustrate this steric effect enhancement from Me to *t*-Bu and the decreasing accessibility of the C2 atom in favour of the C3 and C4 atoms (note the decrease of the green surface in the vicinity of C2 on going from Me to *t*-Bu).

Conclusions

Our work describes the microwave-assisted condensation of 2-aminoindole-3-carbonitriles and their 3-aminoindole-2-

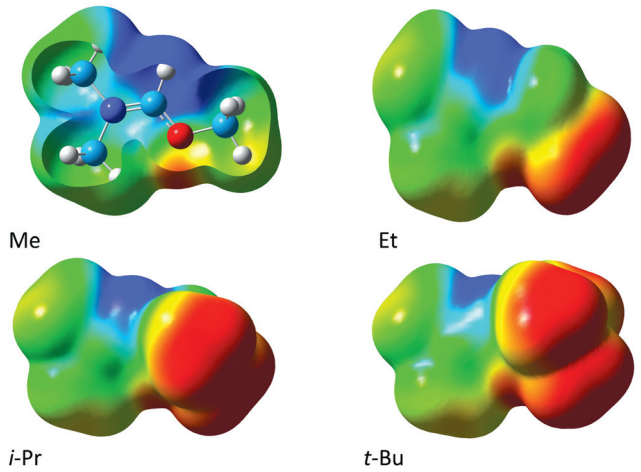


Fig. 1 Molecular electrostatic potential surfaces computed at the SMD/M06-2X/6-31+G(d,p) level of the four alkoxyiminium ions (in the range +0.12 a.u. (blue) to +0.21 a.u. (red).

carbonitrile isomers with various DMF-dialkoxyacetals. Rapid and intense heating of the reaction mixtures was obtained by microwave irradiation. It allowed the appearance of reactive and versatile alkoxyiminium species, which were attacked at their various electrophilic sites by the nucleophilic amines present on the starting scaffolds. *N*,*N*-dimethylformimidamide derivatives were obtained after the first attack of the primary amine on the most electrophilic site (site 1) of the formamide acetals. The second phase of the reaction involves the intracyclic N^1-nitrogen atom of the indole structure. Its nucleophilic attack on the alkoxyiminium ion formed in the mixture was controlled by the steric hindrance of the *O*-alkyl groups. Bulky reagents led to N^1-methylated indoles, confirming the existence of the third electrophilic group of the starting reactant, namely the methyl group linked to the nitrogen atom of formamide. This cascade reaction allowed convenient access to key precursors of building blocks with potential biological activity.

These experimental observations have been rationalised using DFT calculations of theoretical descriptors based on the electrostatic potential. The less favourable approach of the nucleophilic agent to C2 is highlighted by the MEP values, which show the preference for C3/C4 carbon atoms instead of C2 in alkoxyiminium ions that bear crowded *O*-alkyl groups (*i*-Pr and *t*-Bu).

Experimental

General methods for synthesis

The melting points of powder compounds were measured on a STUART-Advanced apparatus. IR spectra were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker DXP 300 spectrometer at 300 and 75 MHz, respectively and a Bruker AVANCE 400 MHz high resolution NMR spectrometer at 400 and 100 MHz, respectively. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Reactions were monitored by TLC analysis using Merck silica gel 60F-254 thin layer plates. Column chromatography was carried out using silica gel Merck 60 (70–230 mesh ASTM). Elemental analyses were found within ±0.4% of the theoretical values. Mass spectra were performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters ZQ 2000 and a Waters LCP 1er XR spectrometer.

Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. Start SYNTH^{TM} (Milestone S.r.l. Italy) is a multi-mode cavity with a microwave power delivery system ranging from 0 to 1200 W. In our case, irradiation at 800 W was sufficient to efficiently reach the programmed temperature (70–140 °C). The temperature was monitored *via* a contact-less infrared pyrometer that was calibrated by control experiments with a fibre-optic contact thermometer protected in a Teflon coated ceramic well inserted directly in the reaction mixture. Open vessel experiments were carried out in a 250 mL round bottom flask fitted with a reflux condenser. The vessel contents were stirred with an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature, pressure and power profiles were monitored in both cases through the EASY-Control software provided by the manufacturer.

Theoretical methods

The simulations have been carried out with the latest version of the Gaussian program.[31] These calculations consisted in geometry optimizations (of several conformations if necessary) of the alkoxyiminium ions and of subsequent vibrational analyses to verify the nature of all geometries. We selected the M06-2X DFT functional to perform our calculations.[32] This global hybrid includes 56% of exact exchange and has been recommended for studying chemical reactivity.[33] A basis set containing diffuse functions, 6-31+G(d,p), was used. The modeling of bulk solvent effects (here *N*,*N*-dimethylformamide, as in the experiments) was included through the use of the recent SMD continuum model.[34] Default algorithms, parameters and thresholds were applied except for (1) the self-consistent field (SCF) convergence threshold, tightened to 10^{-10} a.u.; (2) the force threshold, decreased to 10^{-5} a.u. during all geometry optimizations; (3) the application of an ultra-fine integration grid [pruned (99 590) grid], as it is known that the M06 series of functionals is sensitive to the selected mesh.[35]

The electrostatic potential on the molecular surface, MEP ($V(\boldsymbol{r})$), or at a nucleus, EPN (V_Y), can be determined according to the following formulas (in atomic units, bold characters denote vector quantities):[19]

$$V(\boldsymbol{r}) = \sum_{\mathrm{A}} \frac{Z_{\mathrm{A}}}{|\boldsymbol{R}_{\mathrm{A}} - \boldsymbol{r}|} - \int \frac{\rho(\boldsymbol{r}')\,\mathrm{d}\boldsymbol{r}'}{|\boldsymbol{r}' - \boldsymbol{r}|}$$

$$V_Y \equiv V(\boldsymbol{R}_Y) = \sum_{A \neq Y} \frac{Z_A}{|\boldsymbol{R}_A - \boldsymbol{R}_Y|} - \int \frac{\rho(\boldsymbol{r})\,\mathrm{d}\boldsymbol{r}}{|\boldsymbol{r} - \boldsymbol{R}_Y|}$$

In these equations, Z_{A} is the charge on nucleus A with radius vector $\boldsymbol{R}_{\mathrm{A}}$ and $\rho(\boldsymbol{r})$ is the electronic density function. The first

term in both equations represents the electrostatic potential generated by the atomic nuclei, the second term represents the integration over the continuous distribution of the electronic charge. We have retained these descriptors because the MEP and EPN values reflect the variations of electron densities rigorously, unlike atomic charges, which depend strongly on the particular choice of definition and other approximations. The dominant contribution to V_Y comes from the local densities around the respective atomic sites. More negative V_Y values indicate greater electron densities. The EPN values at the carbon atoms (V_C) have been computed with the Gaussian09 program[31] with tight SCF convergence. For the calculations of the molecular surface electrostatic potentials of the various alkoxyiminiums (V_S), the surfaces of the molecular cations were defined by the 0.002 contour of the electronic density.

General procedure—synthesis of *N*,*N*-dimethylformimidamides (4–7 and 10–13). To a stirred solution of aminoindolecarbonitrile **2**, **3**, **8** or **9** (1.00 mmol) was added DMF-dialkylacetal (**1a–f**, 10.00 mmol) in DMF (2 mL) and the reaction was irradiated at 70–140 °C (800 W) until completion (monitored by TLC). The solution was cooled to room temperature and the mixture was extracted with ethyl acetate. The organic layers were washed with cold water, dried over Na_2SO_4, filtered and evaporated *in vacuo*. A purification by column chromatography over silica gel using dichloromethane–petroleum ether (5 : 5, v/v) as the eluent gave products **4–7** or **10–13** as colored products.

***N*′-(3-Cyano-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (4).** Reaction of 2-amino-1*H*-indole-3-carbonitrile **2** (157 mg, 1.00 mmol) with **1a** (1.4 mL, 10.00 mmol), at 90 °C (800 W) for 15 min, gave **4** (197 mg; 65%) as a yellow powder: mp (neat) 155 °C ± 1 °C; δ_H (DMSO-d_6) 3.09 (3 H, s, NCH_3), 3.17 (3 H, s, NCH_3), 7.11 (2 H, m, *H*-5 and *H*-6), 7.29 (1 H, m, *H*-7), 7.37 (1 H, m, *H*-4), 8.32 (1 H, s, NC*H*N), 11.57 (1 H, *br* s, N*H*); δ_C (DMSO-d_6) 34.1 (2C), 69.9, 110.8, 116.5, 118.1, 120.7, 121.2, 127.7, 132.6, 155.6, 156.2; IR (KBr) ν_{max} 3295, 2198 (CN), 1625, 1551, 1486, 1464, 1417, 1382, 1345, 1304, 1222, 1115, 740, 691 cm^{-1}; HRMS calcd for $C_{12}H_{13}N_4$ $[M + H]^+$ 213.1140 found 213.1143.

***N*′-(3-Cyano-1-methyl-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (5a).** Reaction of 2-amino-1*H*-indole-3-carbonitrile **2** (157 mg, 1.00 mmol) with **1a** (1.4 mL, 10.00 mmol), at 120 °C (800 W) for 45 min, gave **5a** (149 mg; 66%) as a pale brown powder: mp (neat) 130 °C ± 1 °C; δ_H (DMSO-d_6) 3.08 (3 H, s, NCH_3), 3.15 (3 H, s, NCH_3), 3.59 (3 H, s, NCH_3), 7.12 (2 H, m, *H*-5 and *H*-6), 7.36 (2 H, m, *H*-4 and *H*-7), 8.32 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 28.2, 34.2 (2C), 66.8, 109.8, 116.6, 118.4, 121.1, 121.2, 126.8, 133.7, 155.5, 156.4; IR (KBr) ν_{max} 2179 (CN), 1621, 1518, 1482, 1459, 1423, 1414, 1393, 1368, 1343, 1323, 1239, 1122, 1096, 1060, 752, 735 cm^{-1}; HRMS calcd for $C_{13}H_{15}N_4$ $[M + H]^+$ 227.1297 found 227.1292.

***N*′-(3-Cyano-1-ethyl-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (5b).** Reaction of 2-amino-1*H*-indole-3-carbonitrile **2** (157 mg, 1.00 mmol) with **1b** (1.8 mL, 10.00 mmol), at 120 °C (800 W) for 50 min, gave **5b** (159 mg; 66%) as a gold powder: mp (neat) 125 °C ± 1 °C; δ_H (DMSO-d_6) 1.21 (3 H, t, *J* 7.0, CH_2CH_3), 3.08 (3 H, s, NCH_3), 3.15 (3 H, s, NCH_3), 4.15 (2 H, q, *J* 7.0, NCH_2), 7.12 (2 H, m, *H*-5 and *H*-6), 7.38 (2 H, m, *H*-4 and *H*-7), 8.34 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 14.2, 34.1 (2C), 66.8, 36.3, 109.7, 116.7, 118.4, 121.1, 121.2, 127.0, 132.5, 154.9, 156.4; IR (KBr) ν_{max} 2190 (CN), 1622, 1520, 1484, 1466, 1453, 1421, 1409, 1397, 1371, 1342, 1259, 1224, 1200, 1120, 1105, 875, 751, 735 cm^{-1}; HRMS calcd for $C_{14}H_{17}N_4$ $[M + H]^+$ 241.1453 found 241.1443.

***N*′-(1-Benzyl-3-cyano-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (5c).** Reaction of 2-amino-1*H*-indole-3-carbonitrile **2** (157 mg, 1.00 mmol) with **1c** (2.0 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **5c** (197 mg; 65%) as an orange powder: mp (neat) 205 °C ± 1 °C; δ_H (DMSO-d_6) 3.07 (3 H, s, NCH_3), 3.15 (3 H, s, NCH_3), 5.36 (2 H, s, NCH_2), 7.00–7.40 (9 H, m, *H*-4, *H*-5, *H*-6, *H*-7, and Ph-*H*), 8.44 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 34.2 (2C), 44.6, 66.9, 110.3, 116.8, 118.4, 121.3, 121.4, 126.4, 126.6 (2C), 127.1, 128.5 (2C), 132.9, 137.5, 155.2, 156.5; IR (KBr) ν_{max} 2926, 2187 (CN), 1625, 1509, 1496, 1466, 1452, 1398, 1376, 1338, 1187, 1122, 1112, 736, 708, 696, 672, 637 cm^{-1}; HRMS calcd for $C_{19}H_{19}N_4$ $[M + H]^+$ 303.1610 found 303.1600.

***N*′-(3-Cyano-1-propyl-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (5d).** Reaction of 2-amino-1*H*-indole-3-carbonitrile **2** (157 mg, 1.00 mmol) with **1d** (2.0 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **5d** (175 mg; 69%) as a brown powder: mp (neat) 119 °C ± 1 °C; δ_H (DMSO-d_6) 1.21 (3 H, t, *J* 7.0, CH_2CH_3), 1.66 (2 H, m, *J* 7.0, $CH_2CH_2CH_3$), 3.07 (3 H, s, NCH_3), 3.15 (3 H, s, NCH_3), 4.08 (2 H, t, *J* 7.0, NCH_2), 7.10 (2 H, m, *H*-5 and *H*-6), 7.38 (2 H, m, *H*-4 and *H*-7), 8.34 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 11.2, 22.1, 34.1 (2C), 42.8, 66.7, 109.9, 116.7, 118.5, 121.1, 121.2, 126.9, 133.0, 155.3, 156.3; IR (KBr) ν_{max} 2924, 2191, 1622, 1526, 1486, 1465, 1452, 1422, 1385, 1366, 1341, 1328, 1264, 1218, 1202, 1127, 1107, 747, 735 cm^{-1}; HRMS calcd for $C_{15}H_{19}N_4$ $[M + H]^+$ 255.1610 found 255.1600.

***N*′-(3-Cyano-1-isopropyl-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (5e).** Reaction of 2-amino-1*H*-indole-3-carbonitrile **2** (157 mg, 1.00 mmol) with **1e** (2.0 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **5e** (88 mg; 35%) as a yellow powder: mp (neat) 123 °C ± 1 °C; δ_H (DMSO-d_6) 1.50 (6 H, d, *J* 7.0, $CHCH_3$), 3.06 (3 H, s, NCH_3), 3.14 (3 H, s, NCH_3), 5.01 (1 H, m, *J* 7.0, NC*H*), 7.09 (2 H, m, *H*-5 and *H*-6), 7.35 (1 H, m, *H*-7), 7.54 (1 H, m, *H*-4), 8.26 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 20.5 (2C), 34.2 (2C), 45.4, 67.5, 111.2, 116.8, 118.4, 120.8, 121.0, 127.3, 131.9, 155.3, 156.2; IR (KBr) ν_{max} 2919, 2192, 1626, 1607, 1524, 1489, 1464, 1450, 1423, 1388, 1369, 1324, 1138, 1114, 1096, 1060, 735, 707, 690 cm^{-1}; HRMS calcd for $C_{15}H_{19}N_4$ $[M + H]^+$ 255.1610 found 255.1598.

***N*′-(1-(*tert*-Butyl)-3-cyano-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (5f).** Reaction of 2-amino-1*H*-indole-3-carbonitrile **2** (157 mg, 1.00 mmol) with **1f** (2.1 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **5f** (128 mg; 49%) as an orange powder: mp (neat) 137 °C ± 1 °C; δ_H (DMSO-d_6) 1.80 (9 H, s, $(CH_3)_3$), 3.05 (3 H, s, NCH_3), 3.13 (3 H, s, NCH_3), 7.05 (2 H, m, *H*-5 and *H*-6), 7.31 (1 H, m, *H*-7), 7.75 (m, 1H, *H*-4), 8.05 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 30.7 (3C), 34.2 (2C), 60.3, 70.5, 114.3, 116.8, 118.2, 120.6, 120.9, 127.7, 133.6, 154.9,

157.8; IR (KBr) ν_{max} 2924, 2192, 1624, 1604, 1519, 1477, 1458, 1439, 1425, 1401, 1386, 1358, 1321, 1198, 1106, 973, 762, 753, 733 cm^{-1}; HRMS calcd for $C_{16}H_{21}N_4$ $[M + H]^+$ 269.1766 found 269.1767.

***N′*-(3-Cyano-6-nitro-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (6).** Reaction of 2-amino-6-nitro-1*H*-indole-3-carbonitrile **3** (202 mg, 1.00 mmol) with **1a** (1.8 mL, 10.00 mmol), at 70 °C (800 W) for 4 min gave **6** (172 mg; 67%) as a yellow powder: mp (neat) 266 °C ± 1 °C; δ_H (DMSO-d_6) 3.05 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 7.42 (1 H, d, *J* 9.0, *H*-4), 7.93 (1 H, dd, *J* 3.0, 9.0, *H*-6), 7.97 (1 H, s, NC*H*N), 8.35 (1 H, d, *J* 3.0, *H*-7), 12.13 (1 H, *br* s, N*H*); δ_C (DMSO-d_6) 34.3 (2C), 71.9, 106.5, 116.0, 116.1, 116.7, 131.4, 133.9, 141.3, 157.1, 159.4; IR (KBr) ν_{max} 3307, 2206 (CN), 1629, 1500, 1471, 1441, 1402, 1367, 1315, 1299, 1284, 1254, 1222, 1109, 1065, 942, 870, 814, 750, 733, 673 cm^{-1}; HRMS calcd for $C_{12}H_{12}N_5O_2$ $[M + H]^+$ 258.0991 found 258.0991.

***N′*-(3-Cyano-1-methyl-6-nitro-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (7a).** Reaction of 2-amino-6-nitro-1*H*-indole-3-carbonitrile **3** (202 mg, 1.00 mmol) with **1a** (1.4 mL, 10.00 mmol), at 90 °C (800 W) for 30 min, gave **7a** (209 mg; 55%) as an orange powder: mp (neat) 228 °C ± 1 °C; δ_H (DMSO-d_6) 3.13 (3 H, s, NCH_3), 3.20 (3 H, s, NCH_3), 3.69 (3 H, s, NCH_3), 7.48 (1 H, d, *J* 9.0, *H*-4), 8.02 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.31 (1 H, d, *J* 3.0, *H*-7), 8.46 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 28.7, 34.4 (2C), 68.9, 106.2, 116.1, 117.0, 117.1, 132.7, 133.0, 141.4, 157.0, 158.9; IR (KBr) ν_{max} 2207 (CN), 1623, 1604, 1516, 1463, 1322, 1307, 1258, 1215, 1110, 1070, 973, 901, 829, 818, 755, 744, 696, 509 cm^{-1}; HRMS calcd for $C_{13}H_{14}N_5O_2$ $[M + H]^+$ 272.1147 found 272.1151.

***N′*-(3-Cyano-1-ethyl-6-nitro-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (7b).** Reaction of 2-amino-6-nitro-1*H*-indole-3-carbonitrile **3** (202 mg, 1.00 mmol) with **1b** (1.8 mL, 10.00 mmol), at 120 °C (800 W) for 60 min, gave **7b** (214 mg; 75%) as an orange powder: mp (neat) 185 °C ± 1 °C; δ_H (DMSO-d_6) 1.22 (3 H, t, *J* 7.0, CH_2CH_3), 3.11 (3 H, s, NCH_3), 3.19 (3 H, s, NCH_3), 4.23 (2 H, q, *J* 7.0, NCH_2), 7.45 (1 H, d, *J* 9.0, *H*-4), 7.97 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.30 (1 H, d, *J* 3.0, *H*-7), 8.46 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 14.2, 34.3 (2C), 36.8, 68.9, 105.9, 116.2, 116.9, 117.1, 131.4, 133.1, 141.5, 156.9, 158.2; IR (KBr) ν_{max} 3338, 2197 (CN), 1622, 1606, 1525, 1497, 1476, 1375, 1300, 1267, 1204, 1109, 1077, 884, 815, 777, 753, 733 cm^{-1}; HRMS calcd for $C_{14}H_{16}N_5O_2$ $[M + H]^+$ 286.1304 found 286.1315

***N′*-(1-Benzyl-3-cyano-6-nitro-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (7c).** Reaction of 2-amino-6-nitro-1*H*-indole-3-carbonitrile **3** (202 mg, 1.00 mmol) with **1c** (2.0 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **7c** (208 mg; 60%) as a yellow powder: mp (neat) 205 °C ± 1 °C; δ_H (DMSO-d_6) 3.10 (3 H, s, NCH_3), 3.20 (3 H, s, NCH_3), 5.50 (2 H, s, NCH_2), 7.26 (5 H, m, Ph-*H*), 7.50 (d, 1 H, *J* = 9 Hz, *H*-4), 7.98 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.25 (1 H, d, *J* 3.0, *H*-7), 8.58 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 34.4 (2C), 44.7, 69.0, 106.3, 116.4, 117.0, 117.2, 127.1 (2C), 127.5, 128.7 (2C), 131.8, 133.2, 136.9, 141.5, 157.2, 158.7; IR (KBr) ν_{max} 2200 (CN), 1624, 519, 1499, 1475, 1456, 1428, 1399, 1315, 1256, 1113, 1084, 1075, 882, 816, 811, 750, 732, 714, 695, 653 cm^{-1}; HRMS calcd for $C_{19}H_{18}N_5O_2$ $[M + H]^+$ 348.1461 found 348.1459.

***N′*-(3-Cyano-6-nitro-1-propyl-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (7d).** Reaction of 2-amino-6-nitro-1*H*-indole-3-carbonitrile **3** (202 mg, 1.00 mmol) with **1d** (2.0 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **7d** (215 mg; 72%) as an orange powder: mp (neat) 170 °C ± 1 °C; δ_H (DMSO-d_6) 0.85 (3 H, t, *J* 7.0, CH_2CH_3), 1.69 (2 H, m, *J* 7.0, CH_2CH_3), 3.11 (3 H, s, NCH_3), 3.19 (3 H, s, NCH_3), 4.19 (2 H, t, *J* 7.0, NCH_2), 7.48 (1 H, d, *J* 9.0, *H*-4), 7.99 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.35 (1 H, d, *J* 3.0, *H*-7), 8.48 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 11.1, 22.1, 34.3 (2C), 43.2, 68.9, 106.2, 116.2, 116.9, 117.1, 132.0, 133.0, 141.5, 156.9, 158.7; IR (KBr) ν_{max} 2929, 2202, 1621, 1605, 1521, 1497, 1475, 1461, 1399, 1374, 1298, 1260, 1202, 1126, 1107, 1077, 967, 879, 814, 753, 734, 715 cm^{-1}; HRMS calcd for $C_{15}H_{18}N_5O_2$ $[M + H]^+$ 300.1461 found 300.1464.

***N′*-(3-Cyano-1-isopropyl-6-nitro-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (7e).** Reaction of 2-amino-6-nitro-1*H*-indole-3-carbonitrile (202 mg, 1.00 mmol) with **1e** (2.0 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **7e** (117 mg; 39%) as an orange powder: mp (neat) 184 °C ± 1 °C; δ_H (DMSO-d_6) 1.54 (6 H, d, *J* 7.0, $CHCH_3$), 3.12 (3 H, s, NCH_3), 3.19 (3 H, s, NCH_3), 5.11 (1 H, m, *J* 7.0, NC*H*), 7.51 (1 H, d, *J* 9.0, *H*-4), 8.02 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.42 (2 H, m, *H*-7 and NC*H*N); δ_C (DMSO-d_6) 20.6 (2C), 34.4 (2C), 46.5, 69.8, 106.8, 116.4, 116.7, 117.0, 130.9, 133.3, 141.3, 156.7, 159.0; IR (KBr) ν_{max} 2919, 2202, 1622, 1603, 1520, 1495, 1471, 1372, 1299, 1273, 1258, 1221, 1128, 1102, 1079, 970, 879, 813, 753, 743, 734, 711 cm^{-1}; HRMS calcd for $C_{15}H_{18}N_5O_2$ $[M + H]^+$ 300.1461 found 300.1472.

***N′*-(1-(*tert*-Butyl)-3-cyano-6-nitro-1*H*-indol-2-yl)-*N*,*N*-dimethylformimidamide (7f).** Reaction of 2-amino-6-nitro-1*H*-indole-3-carbonitrile (202 mg, 1.00 mmol) with **1f** (2.1 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **7f** (41 mg; 13%) as an orange powder: mp (neat) 218 °C ± 1 °C; δ_H (DMSO-d_6) 1.87 (9 H, s, $(CH_3)_3$), 3.10 (3 H, s, NCH_3), 3.18 (3 H, s, NCH_3), 7.46 (1 H, d, *J* 9.0, *H*-4), 8.00 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.25 (1 H, s, NC*H*N), 8.63 (1 H, d, *J* 3.0, *H*-7); δ_C (DMSO-d_6) 30.3 (3C), 34.5 (2C), 61.9, 72.3, 110.2, 116.2, 116.4, 116.9, 132.1, 133.8, 141.1, 155.7, 161.3; IR (KBr) ν_{max} 2929, 2192, 1621, 1525, 1500, 1468, 1440, 1373, 1310, 1288, 1259, 1224, 1187, 1169, 1087, 870, 820, 751, 735, 710 cm^{-1}; HRMS calcd for $C_{16}H_{20}N_5O_2$ $[M + H]^+$ 314.1617 found 314.1623.

***N′*-(2-Cyano-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (10).** Reaction of 3-amino-1*H*-indole-2-carbonitrile **8** (157 mg, 1.00 mmol) with **1a** (1.4 mL, 10.00 mmol), at 90 °C (800 W) for 15 min, gave **10** (91 mg; 43%) as a red oil; δ_H (DMSO-d_6) 3.00 (3 H, s, NCH_3), 3.06 (3 H, s, NCH_3), 7.04 (1 H, ddd, *J* 2.0, 7.0, 8.0, *H*-6), 7.28 (1 H, ddd, *J* 2.0, 7.0, 8.0, *H*-5), 7.29 (1 H, d, *J* 9.0, *H*-7), 7.65 (1 H, d, *J* 9.0, *H*-4), 8.08 (1 H, s, NC*H*N), 11.43 (1 H, *br* s, N*H*); δ_C (DMSO-d_6) 34.0 (2C), 94.8, 112.1, 116.0, 119.5, 120.3, 120.6, 125.8, 136.6, 141.1, 154.9; IR (KBr) ν_{max} 2921, 2852, 2204 (CN), 1688, 1615, 1463, 1376, 1226, 1095, 971, 880, 740 cm^{-1}; HRMS calcd for $C_{12}H_{13}N_4$ $[M + H]^+$ 213.1140 found 213.1129.

***N′*-(2-Cyano-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (11a).** Reaction of 3-amino-1*H*-indole-2-carbonitrile **8** (157 mg, 1.00 mmol) with **1a** (1.4 mL, 10.00 mmol), at 90 °C (800 W) for 30 min, gave **11a** (174 mg; 77%) as a red oil; δ_H (DMSO-d_6) 3.06 (3 H, s, NCH_3), 3.12 (3 H, s, NCH_3), 3.79 (3 H, s, NCH_3), 7.12 (1 H, ddd, *J* 2.0, 7.0, 8.0, *H*-6), 7.41 (1 H, ddd, *J* 2.0, 7.0, 8.0, *H*-5), 7.53 (1 H, d, *J* 9.0, *H*-7), 7.73 (1 H, d, *J* 9.0, *H*-4), 8.15 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 30.9, 33.8 (2C), 99.0, 110.5, 115.0, 119.6, 120.3, 120.6, 126.0, 137.4, 140.8, 154.8; IR (KBr) ν_{max} 3242, 2922, 2201 (CN), 1623, 1532, 1462, 1434, 1368, 1323, 1259, 1239, 1095, 971, 837, 741, 674 cm^{-1}; HRMS calcd for $C_{13}H_{15}N_4$ $[M + H]^+$ 227.1297 found 227.1290.

***N′*-(2-Cyano-1-ethyl-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (11b).** Reaction of 3-amino-1*H*-indole-2-carbonitrile **8** (157 mg, 1.00 mmol) with **1b** (1.8 mL, 10.00 mmol), at 140 °C (800 W) for 60 min, gave **11b** (173 mg; 72%) as an orange oil; δ_H (DMSO-d_6) 1.27 (3 H, t, *J* 7.0, CH_2CH_3), 3.00 (3 H, s, NCH_3), 3.06 (3 H, s, NCH_3), 4.21 (2 H, q, *J* 7.0, NCH_2), 7.06 (1 H, ddd, *J* 2.0, 7.0, 8.0, *H*-6), 7.35 (1 H, ddd, *J* 2.0, 7.0, 8.0, *H*-5), 7.51 (1 H, d, *J* 9.0, *H*-7), 7.68 (1 H, d, *J* 9.0, *H*-4), 8.10 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 15.1, 33.8 (2C), 61.4, 97.6, 110.4, 114.9, 119.6, 120.6, 120.7, 126.0, 136.3, 141.2, 154.9; IR (KBr) ν_{max} 2926, 2199 (CN), 1623, 1588, 1561, 1537, 1447, 1398, 1367, 1346, 1324, 1257, 1227, 1192, 1102, 1062, 1043, 971, 741, 676, 635 cm^{-1}; HRMS calcd for $C_{14}H_{17}N_4$ $[M + H]^+$ 241.1453 found 241.1444.

***N′*-(1-Benzyl-2-cyano-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (11c).** Reaction of 3-amino-1*H*-indole-2-carbonitrile **8** (157 mg, 1.00 mmol) with **1c** (2.0 mL, 10.00 mmol), at 140 °C (800 W) for 60 min, gave **11c** (196 mg; 65%) as an orange oil; δ_H (DMSO-d_6) 3.00 (3 H, s, NCH_3), 3.06 (3 H, s, NCH_3), 5.42 (2 H, s, NCH_2), 7.06 (1 H, ddd, *J* 2.0, 7.0, 8.0, *H*-6), 7.22 (6 H, m, Ph-*H* and *H*-5), 7.57 (1 H, d, *J* 9.0, *H*-7), 7.70 (1 H, d, *J* 9.0, *H*-4), 8.12 (1 H, s, NC*H*N); δ_C (DMSO-d_6) 33.8 (2C), 47.5, 98.3, 110.9, 115.1, 119.9, 120.7, 126.3, 126.7 (2C), 127.6, 128.0, 128.7 (2C), 137.0, 137.3, 141.6, 155.1; IR (KBr) ν_{max} 2921, 2200 (CN), 1623, 1609, 1452, 1422, 1367, 1345, 1320, 1250, 1186, 1102, 969, 740, 721, 695, 676, 635, 612 cm^{-1}; HRMS calcd for $C_{19}H_{19}N_4$ $[M + H]^+$ 303.1610 found 303.1604.

***N′*-(2-Cyano-5-nitro-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (12).** Reaction of 3-amino-5-nitro-1*H*-indole-2-carbonitrile **9** (202 mg, 1.00 mmol) with **1b** (1.8 mL, 10.00 mmol), at 90 °C (800 W) for 10 min, gave **12** (160 mg; 63%) as a red powder: mp (neat) 193 °C ± 1 °C; δ_H (DMSO-d_6) 3.05 (3 H, s, NCH_3), 3.10 (3 H, s, NCH_3), 7.47 (1 H, d, *J* 9.0, *H*-7), 8.12 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.15 (1 H, s, NC*H*N), 8.53 (d, 1 H, *J* 3.0, *H*-4), 12.26 (1 H, *br* s, N*H*); δ_C (DMSO-d_6) 33.9 (2C), 96.9, 112.8, 114.8, 117.9, 120.2, 120.5, 138.6, 140.8, 143.3, 155.5; IR (KBr) ν_{max} 3237, 2209 (CN), 1633, 1612, 1582, 1519, 1479, 1323, 1273, 1259, 1226, 1157, 1102, 1062, 979, 844, 798, 739, 691, 679, 637 cm^{-1}; HRMS calcd for $C_{12}H_{12}N_5O_2$ $[M + H]^+$ 258.0991 found 258.0978.

***N′*-(2-Cyano-1-methyl-5-nitro-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (13a).** Reaction of 3-amino-5-nitro-1*H*-indole-2-carbonitrile **9** (202 mg, 1.00 mmol) with **1a** (1.4 mL, 10.00 mmol), at 70 °C (800 W) for 2 min, gave **13a** (209 mg; 77%) as a red powder: mp (neat) 194 °C ± 1 °C; δ_H (DMSO-d_6) 3.05 (3 H, s, NCH_3), 3.11 (3 H, s, NCH_3), 3.83 (3 H, s, NCH_3), 7.68 (1 H, d, *J* 9.0, *H*-7), 8.16 (1 H, s, NC*H*N), 8.17 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.54 (1 H, d, *J* 3.0, *H*-4); δ_C (DMSO-d_6) 31.7, 34.0 (2C), 101.1, 111.4, 113.9, 118.0, 119.8, 120.5, 139.0, 140.7, 143.1, 155.5; IR (KBr) ν_{max} 2927, 2204 (CN), 1623, 1603, 1515, 1478, 1458, 1394, 1320, 1303, 1274, 1258, 1225, 1110, 1070, 977, 902, 816, 755, 744, 698 cm^{-1}; HRMS calcd for $C_{13}H_{14}N_5O_2$ $[M + H]^+$ 272.1147 found 272.1149.

***N′*-(2-Cyano-1-ethyl-5-nitro-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (13b).** Reaction of 3-amino-5-nitro-1*H*-indole-2-carbonitrile **9** (202 mg, 1.00 mmol) with **1b** (1.8 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **13b** (241 mg; 86%) as an orange powder: mp (neat) 146 °C ± 1 °C; δ_H (DMSO-d_6) 1.32 (3 H, t, *J* 7.0, CH_2CH_3), 3.05 (3 H, s, NCH_3), 3.11 (3 H, s, NCH_3), 4.30 (2 H, q, *J* 7.0, NCH_2), 7.70 (1 H, d, *J* 9.0, *H*-7), 8.12 (1 H, dd, *J* 3.0, 9.0, *H*-6), 8.15 (1 H, s, NC*H*N), 8.48 (1 H, d, *J* 3.0, *H*-4); δ_C (DMSO-d_6) 15.0, 33.9 (2C), 62.1, 99.6, 111.2, 113.9, 118.0, 120.1, 120.5, 138.0, 140.7, 143.4, 155.5; IR (KBr) ν_{max} 2927, 2199 (CN), 1623, 1603, 1516, 1463, 1392, 1322, 1307, 1291, 1257, 1215, 1110, 1070, 1058, 973, 901, 873, 818, 744, 696 cm^{-1}; HRMS calcd for $C_{14}H_{16}N_5O_2$ $[M + H]^+$ 286.1304 found 286.1301.

***N′*-(1-Benzyl-2-cyano-5-nitro-1*H*-indol-3-yl)-*N*,*N*-dimethylformimidamide (13c).** Reaction of 3-amino-5-nitro-1*H*-indole-2-carbonitrile **9** (202 mg, 1.00 mmol) with **1c** (2.0 mL, 10.00 mmol), at 120 °C (800 W) for 30 min, gave **13c** (330 mg; 95%) as an orange powder: mp (neat) 197 °C ± 1 °C; δ_H (DMSO-d_6) 3.05 (3 H, s, NCH_3), 3.11 (3 H, s, NCH_3), 5.54 (2 H, s, NCH_2), 7.18 (2 H, dd, Ph-*H*), 7.32 (3 H, m, Ph-*H*), 7.83 (1 H, d, *J* 9.0, *H*-7), 8.17 (1H, dd, *J* 3.0, 9.0, *H*-6), 8.19 (1 H, s, NC*H*N), 8.56 (1 H, d, *J* 3.0, *H*-4); δ_C (DMSO-d_6) 34.0 (2C), 48.2, 100.3, 111.7, 114.0, 118.2, 120.3, 121.0, 126.7 (2C), 127.9, 128.8 (2C), 136.5, 138.9, 141.0, 143.7, 155.7; IR (KBr) ν_{max} 2978, 2199 (CN), 1623, 1600, 1510, 1454, 1392, 1364, 1316, 1297, 1275, 1189, 1108, 1068, 971, 810, 739, 714, 676, 638 cm^{-1}; HRMS calcd for $C_{19}H_{18}N_5O_2$ $[M + H]^+$ 348.1461 found 348.1451.

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