Selective Methylation of NH-Containing Heterocycles and Sulfonamides Using *N*,*N*-Dimethylformamide Dimethylacetal Based on Calculated pK_a Measurements

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Abstract: The use of *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) as a suitable methylating agent for the methylation of NH-containing groups and heterocycles has been investigated. Use of ReactArray and calculated pK_a measurements have allowed additional helpful information to be collated to determine optimum reaction conditions for a variety of substrates.

Key words: methylation, *N*,*N*-dimethylformamide dimethylacetal, heterocycles, sulfonamides, pK_a

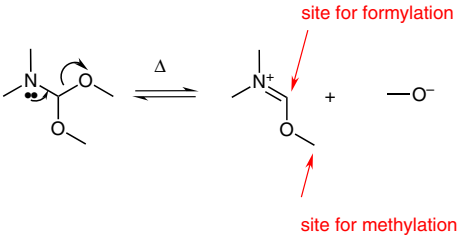
Methylation of NH-containing heterocycles is a widely performed transformation within synthetic chemistry. Traditional reagents such as methyl iodide and dimethylsulfate are widely used, however, these have undesirable safety aspects mainly associated with their carcinogenic properties. Practical issues include difficulty of handling these reagents on small scale, over methylation due to their reactive nature and regioselectivity, such as when oxygen and sulfur are also present in the structure.

The use of DMF-DMA as a suitable methylating agent has been widely reported in the literature for the synthesis of esters from carboxylic acids,[1] ethers from phenols,[2] and thioethers from aromatic thiols.[3] However, methylation of NH-containing heterocycles has been less widely reported, these have mainly included amidic-based structures such as uracil derivatives.[4] A notable exception was by B. Stanovnik et al.[5] who reported methylation of a number of heterocycles bearing SH, NH, and/or OH groups.

DMF-DMA can react via two different pathways, one leading to methylation and the other leading to condensation products such as *N*,*N*-dimethyl enaminones (protected formyl group, Scheme 1). Depending on the choice of substrate, the benefits of the reaction are that DMF-DMA generates its own base (methoxide) and the byproducts are easily removed by standard evaporation techniques.

Recent work within our group had shown indole and related azaindole-based scaffolds to be suitable substrates for the NH methylation with DMF-DMA. This led us to further investigate this reaction.

The following (aza)-indoles, 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**6**), 3-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (**11**), and 3-phenyl-1*H*-indole (**13**) were chosen as suitable substrates for investigation based on ease of synthesis or availability in our local building-block collection (Figure 1). Crucially, they all have blocking groups at C3 to avoid the formylation reaction pathway.



Scheme 1 Electrophilic sites for methylation and formylation

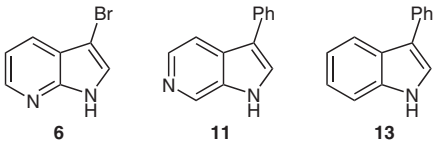


Figure 1 Substrates chosen for investigation

To determine the temperature required for methylation to occur with the three chosen substrates as well as confirming alkylation on N1 for substrates **6** and **11**, a small scale trial was carried out utilizing DMF-DMA in DMF as the reaction solvent. Results of this are shown in Table 1.

The ReactArray optimizer[6,7] was chosen as a suitable automation platform to aid further investigation of this reaction. It was decided that the main benefits of the reaction were its simplistic nature, therefore the two main parameters to be investigated were time and temperature. Samples for LC–MS analysis were automatically taken at three hour time points during a 24 hour time period for LC–MS analysis and the following graphs plotted for ease of analysis of data (Figure 2).

The data obtained from these experiments showed that complete reaction occurred as long as the temperature was of the required level. Failure to reach this temperature resulted in incomplete reaction presumably due to either degradation of reagent or gradual loss through evaporation from the vessel. An additional ReactArray experiment using **6** which investigated time vs. the number of equivalents of DMF-DMA also showed the reaction pro-

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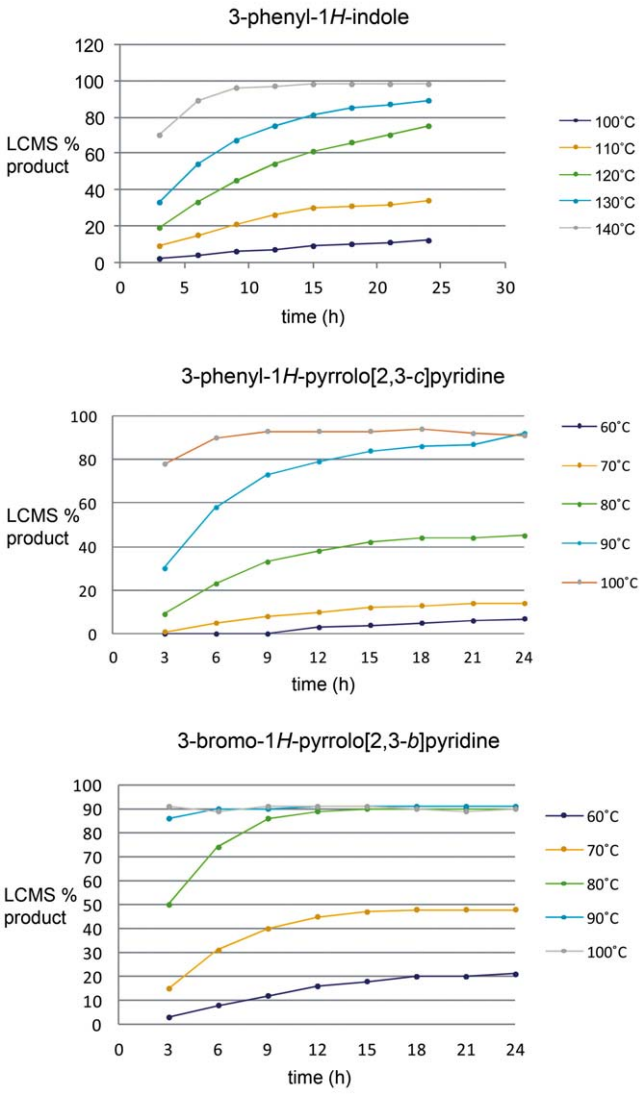


Figure 2 ReactArray data plots, time vs. product (%) at a variety of temperatures over a 24 hour time period

gressed to completion with only a twofold excess of reagent (Figure 3).

With this data in hand, it was deemed that there may be a correlation between pK_a of NH that was to be methylated and temperature required for methylation to proceed to completion. In general, the lower the pK_a, the lower the

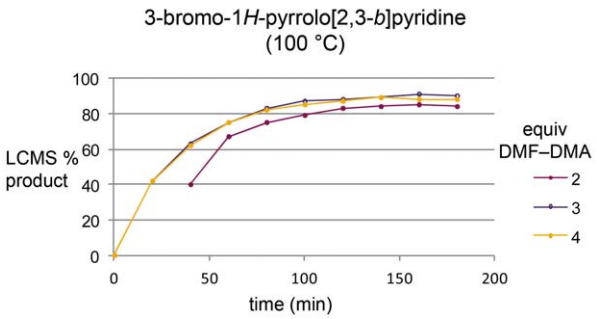


Figure 3 ReactArray data plot, time vs. product (%) at 100 °C with two, three, and four equivalents of DMF-DMA

temperature required for methylation to take place. Based on this data a small selection of heterocycles were subjected to DMF-DMA at a temperature determined based on the calculated pK_a of the NH to be methylated. Results are shown in Table 1.

This showed some interesting results, all heterocycles gave moderate to good yields – carried out at a temperature based on purely calculated pK_a.[8] With regards to entry 6 and 11 (Table 1), no methylation was observed on pyridine-ring nitrogens, N7 and N6, respectively. Most notable were entries 1 and 12 (Table 1) whereby regioselective methylation could be obtained with methylation occurring at 60 °C on the more acidic sulfonamide NH in excellent yield, dimethylation can be obtained by simply raising the temperature, in this case 110 °C was chosen based on pK_a calculations. Acyclic amides did not methylate under the conditions chosen but this could be used to an advantage as selective methylation can occur on additional NH sites. Entries 3 and 7 (Table 1) show methylation on sulfonamide and indole NH, respectively, in good yield. Entries 5 and 9 (Table 1) gave mixtures of N1 and N2 methylation which were separated showing a 5:4 ratio in favor of N2 methylation for entry 5 and a 2:1 ratio of N1 methylation for entry 9. Unfortunately, Boc-protected amines (Table 1, entry 14) did not undergo methylation presumably due to sterics, and increase of temperature gave an unwanted methylcarbamate side product. This may well have formed via base-mediated isocyanate formation and subsequent attack by methanol or methoxide.[9] Cyclic ureas underwent methylation in good yields with no O-methylation observed (Table 1, entry 4).

Table 1 Methylations Using DMF-DMA (5 equiv) in DMF at a Specific Temperature Based on Calculated pK_a

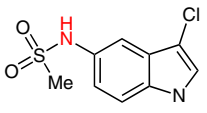
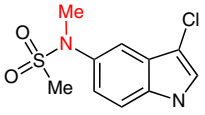
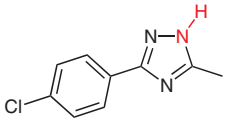
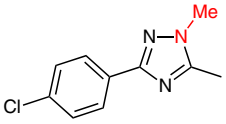
Entry	Heterocycle	Product	Calcd pK_a (+/– 0.5)	Temp (°C)	Yield (%)[a]
1			8.6 ($NHSO_2Me$) 15.9 (indole NH)	60	83
2			10.3	60	62

Table 1 Methylations Using DMF-DMA (5 equiv) in DMF at a Specific Temperature Based on Calculated pK_a (continued)

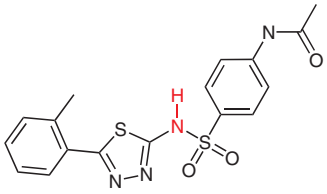
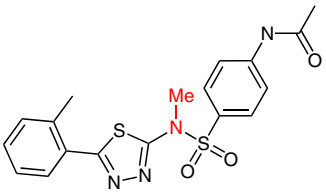
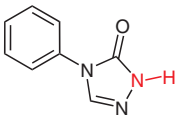
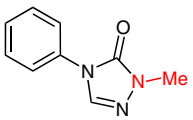
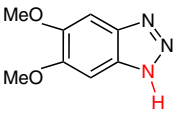
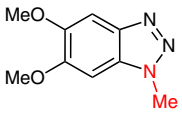
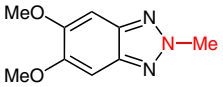
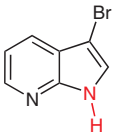
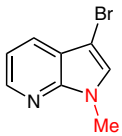
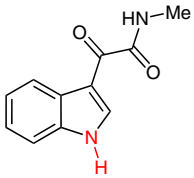
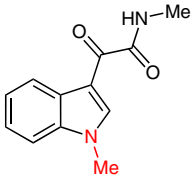
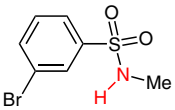
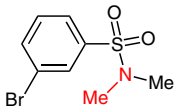
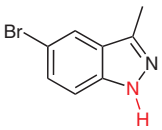
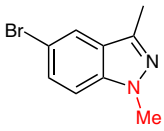
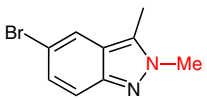
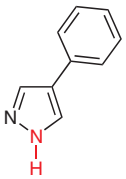
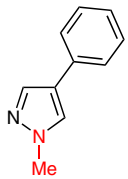
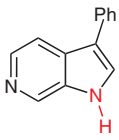
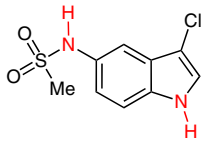
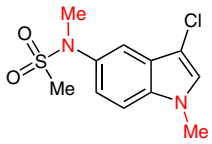
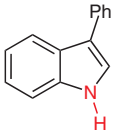
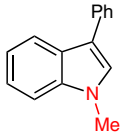
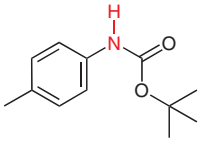
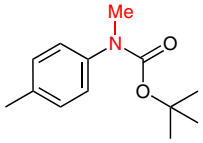
Entry	Heterocycle	Product	Calcd pK_a (+/– 0.5)	Temp (°C)	Yield (%)[a]
3			5.1	60	60[b]
4[10]			9.5	70	78
5			8.3	70	39
		5a			
					50
		5b			
6			12.2	80	76
7			15.1	80	87
8[10]			10.9	80	92
9			13.1	90	43
		9a			
					27[c]
		9b			
10			13.9	90	41
11[10]			14.4	100	73

Table 1 Methylations Using DMF-DMA (5 equiv) in DMF at a Specific Temperature Based on Calculated pK_a (continued)

Entry	Heterocycle	Product	Calcd pK_a (+/– 0.5)	Temp (°C)	Yield (%)[a]
12			8.6 ($NHSO_2Me$) 15.9 (indole NH)	110	52
13[10]			16.7	120	87
14			13.9	120	0

[a] Isolated yield.
[b] 21% starting material remained after 2 d at 60 °C.
[c] Product inseparable from remaining starting material, yield based on ^{1}HNMR analysis showing purity of 58%.

In summary, DMF-DMA is an excellent methylating agent for NH-containing heterocycles as well as sulfonamides. Using calculated pK_a values allowed a rough prediction of temperature required for methylation to occur enabling a right first-time approach.

This pK_a–temperature correlation (Table 2) allows the potential for regioselective methylations to take place which may have added benefits over traditional methylating conditions. The possibility of two different reaction pathways is key to choosing whether the substrate may be acceptable for methylation. The simplistic nature of the reaction is one of the true benefits as it is very straightforward to perform on both small scale and large scale with an easy-to-handle reagent and simple workup procedures.

Table 2 Approximate Temperature to Trial for DMF-DMA Methylation Based on Calculated pK_a

Calcd pK_a	Temp (°C)
8	50
9	60
10	70
11	80
12	90
13	100
14	110
15	120
16	130
17	140

Acknowledgment

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References and Notes

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(10) **General Procedure**:
To a stirred solution of substrate in dry DMF was added DMF-DMA (5 equiv) in one portion at r.t. The resulting mixture was heated at a temperature (60–120 °C) based on calculated pK_a (Table 2) for approximately 18 h and allowed to cool to r.t. The reaction mixture was evaporated to dryness and purified by flash silica chromatography.
2-Methyl-4-phenyl-1,2,4-triazol-3-one (4)
Temp 70 °C; yield 78%; white solid; MS (ES$^+$): *m/z* [M + H]$^+$ = 176.33; HPLC: t_R= 1.02 min. ^{1}H NMR (700 MHz, DMSO): δ = 8.43 (s, 1 H), 7.67 (dt, *J* = 8.7, 1.7 Hz, 2 H), 7.48–7.52 (m, 2 H), 7.35–7.38 (m, 1 H), 3.38 (s, 3 H). ^{13}C NMR (176 MHz, DMSO): δ = 151.31, 134.59, 134.11, 129.32, 127.00, 121.48, 32.10.
3-Bromo-*N*,*N*-dimethyl-benzenesulfonamide (8)
Temp 80 °C; yield 92%; white solid; HRMS: *m/z* [M + H]$^+$ calcd for $C_8H_{10}BrNO_2S$: 263.96939; found: 263.96875. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (t, *J* = 1.8 Hz, 1 H), 7.62–7.69 (m, 2 H), 7.35 (t, *J* = 7.9 Hz, 1 H), 2.67 (s, 6 H).
1-Methyl-3-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (11)
Temp 100 °C; yield 73%; beige solid; MS (ES$^+$): *m/z* [M +

H]$^+$ = 209.41. HPLC: t_R = 2.13 min. ^{1}H NMR (400 MHz, DMSO): δ = 8.90 (s, 1 H), 8.23 (d, *J* = 5.6 Hz, 1 H), 7.95 (s, 1 H), 7.83 (dd, *J* = 5.6, 1.0 Hz, 1 H), 7.69 (dd, *J* = 8.3, 1.2 Hz, 2 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (101 MHz, DMSO, 30 °C): δ = 138.71, 134.37, 134.12, 133.72, 131.18, 129.26, 128.87, 126.21, 125.70, 114.23, 113.58, 32.79.

1-Methyl-3-phenylindole (13)

Temp 120 °C; yield 87%; colorless gum; HRMS: *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}N$: 207.1048; found: 207.1027. ^{1}H NMR (400 MHz, DMSO): δ = 7.88 (d, *J* = 8.0 Hz, 1 H), 7.64–7.7 (m, 3 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 7.40–7.47 (m, 2 H), 7.20–7.27 (m, 2 H), 7.11–7.17 (m, 1 H), 3.85 (s, 3 H).

