Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Design of Experiments (DoE) Reaction Optimisation and Solvent Selection: A Guide for Academic Chemists

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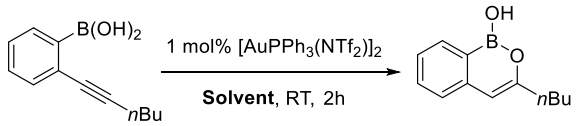
1. Experimental Procedures, Data and Spectra for Solvent Substitution Reactions

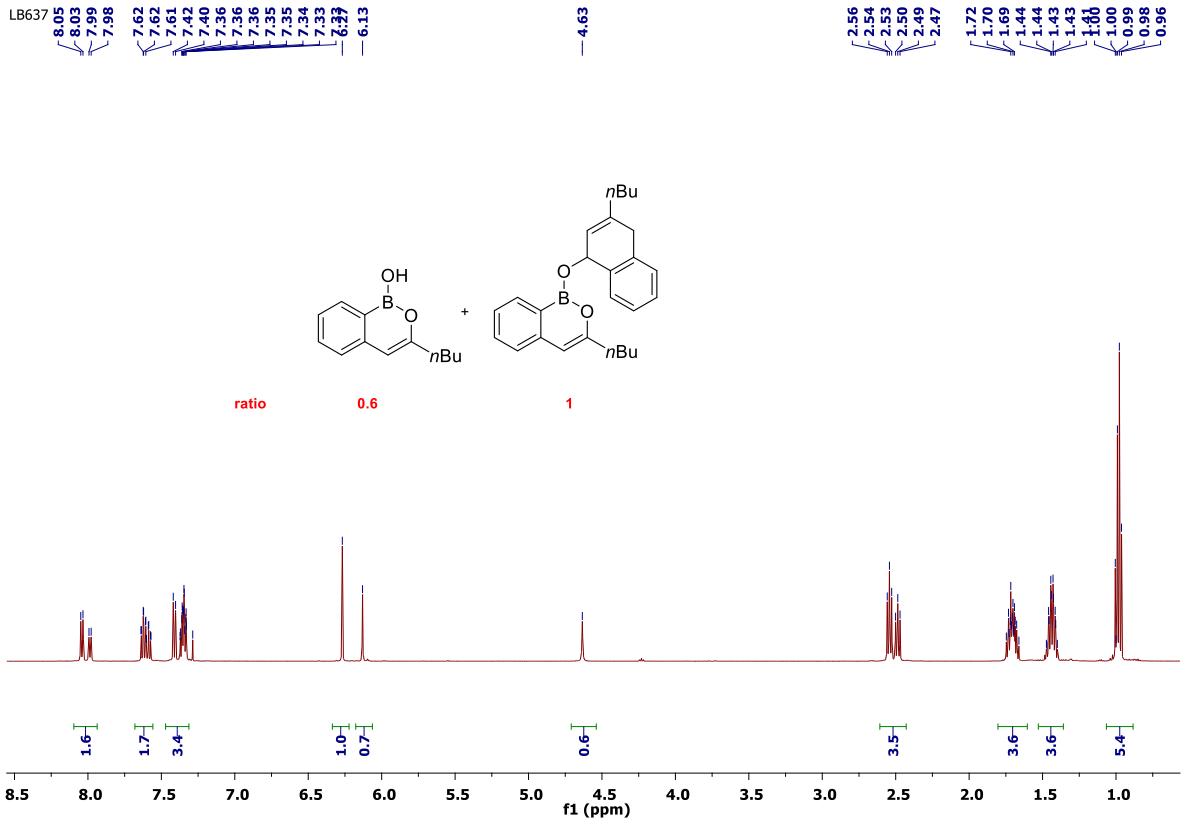
Experimental procedures

Gold catalysed synthesis of boron enolate from alkynes[1]



Entry	Solvent	Yields (%)
1	CH_2Cl_2	80
2	MeO_2CO_2Me	84

General procedure: $[Au(PPh_3)(NTf_2)]_2$.PhMe (8 mg, 0.005 mmol) was added to a solution of 2-(hex-1-ynyl)phenylboronic acid (100 mg, 0.5 mmol) in the solvent (0.6 mL). The solution was stirred at room temperature for 3 hours. The mixture was then directly loaded onto a column and purified via chromatography on silica gel using Petrol/EtOAc (100/0 to 80/20) as eluent. Evaporation of the solvent afforded a mixture of monomeric and dimeric boron enolate product (ratio 0.6/1) as a colourless oil; ^{1}H NMR ($CDCl_3$, 500 MHz, monomer) δ = 7.98 (d, 1H, *J* = 7.4 Hz, C*H*$_{Ar}$), 7.60 (td, 1H, *J* = 7.7, 1.4 Hz, C*H*$_{Ar}$), 7.35-7.31 (m, 2H, C*H*$_{Ar}$), 6.13 (s, 1H, =C*H*), 4.63 (br, 1H, BO*H*), 2.49 (t, 2H, *J* = 7.4 Hz, C*H*$_2$($CH_2CH_2CH_3$)), 1.71(q, 2H, *J* = 7.7 Hz, C*H*$_2$(CH_2CH_3)), 1.44 (sext, 2H, *J* = 7.6 Hz, C*H*$_2$$CH_3$) 0.99 (t, 3H, *J* = 7.4 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 500 MHz) δ = 155.2, 143.3, 132.5, 132.3, 125.4, 124.9, 105.5, 34.7, 29.4, 22.3, 13.9, the carbon adjacent to boron was not observed. These data are in agreement with the data reported in the literature.[1]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2.53
2.50
2.49
2.47
1.72
1.70
1.69
1.44
1.43
1.43
1.41
1.00
0.99
0.98
0.96
nBu
OH
B
O
nBu
+
O
B
O
nBu
ratio
0.6
1
1.6
1.7
3.4
1.0
0.7
0.6
3.5
3.6
3.6
5.4
8.5
8.0
7.5
7.0
6.5
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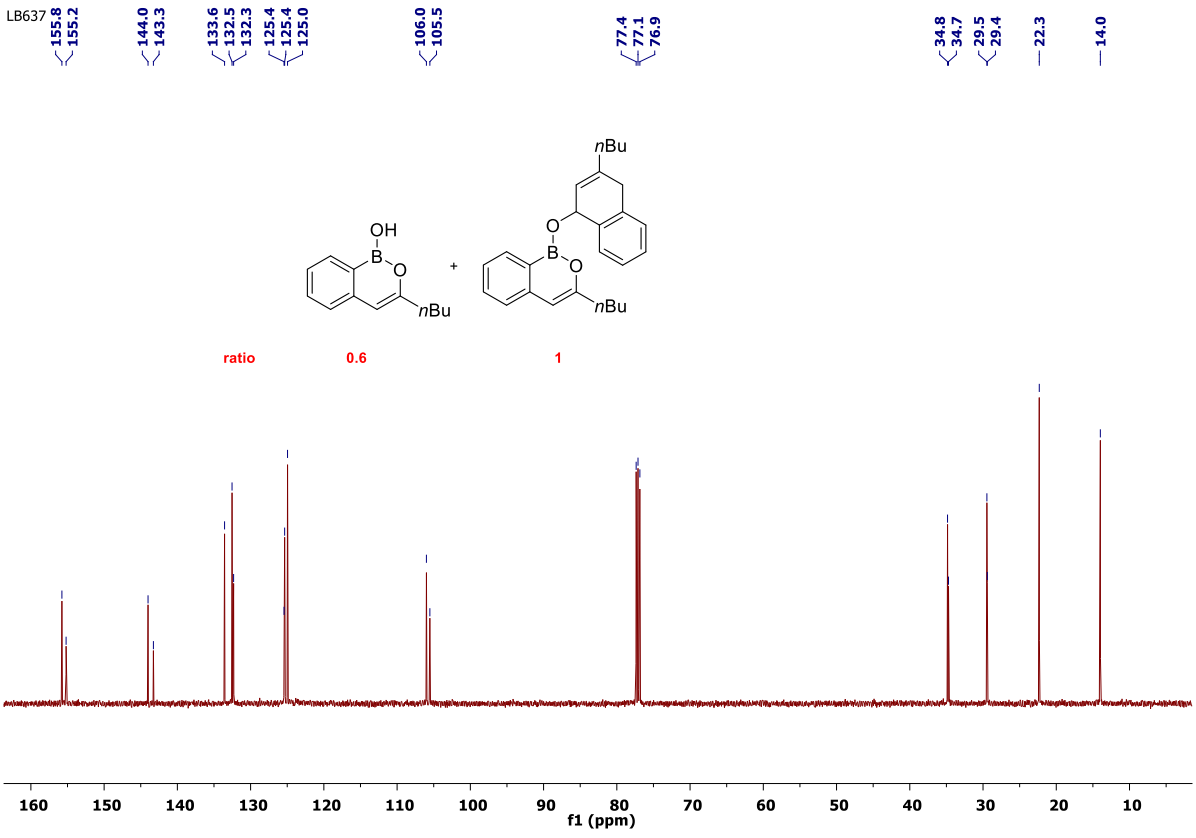
2.0
1.5
1.0
f1 (ppm)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105.5
77.4
77.1
76.9
34.8
34.7
29.5
29.4
22.3
14.0
nBu
OH
B
O
nBu
+
O
B
O
nBu
ratio
0.6
1
160
150
140
130
120
110
100
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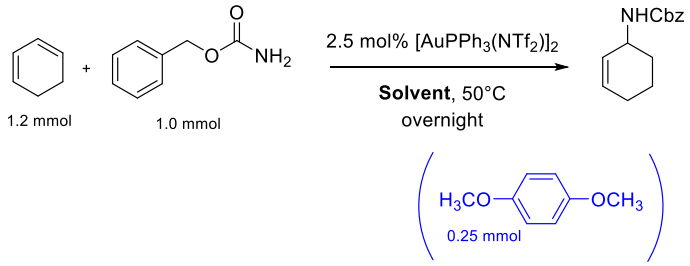
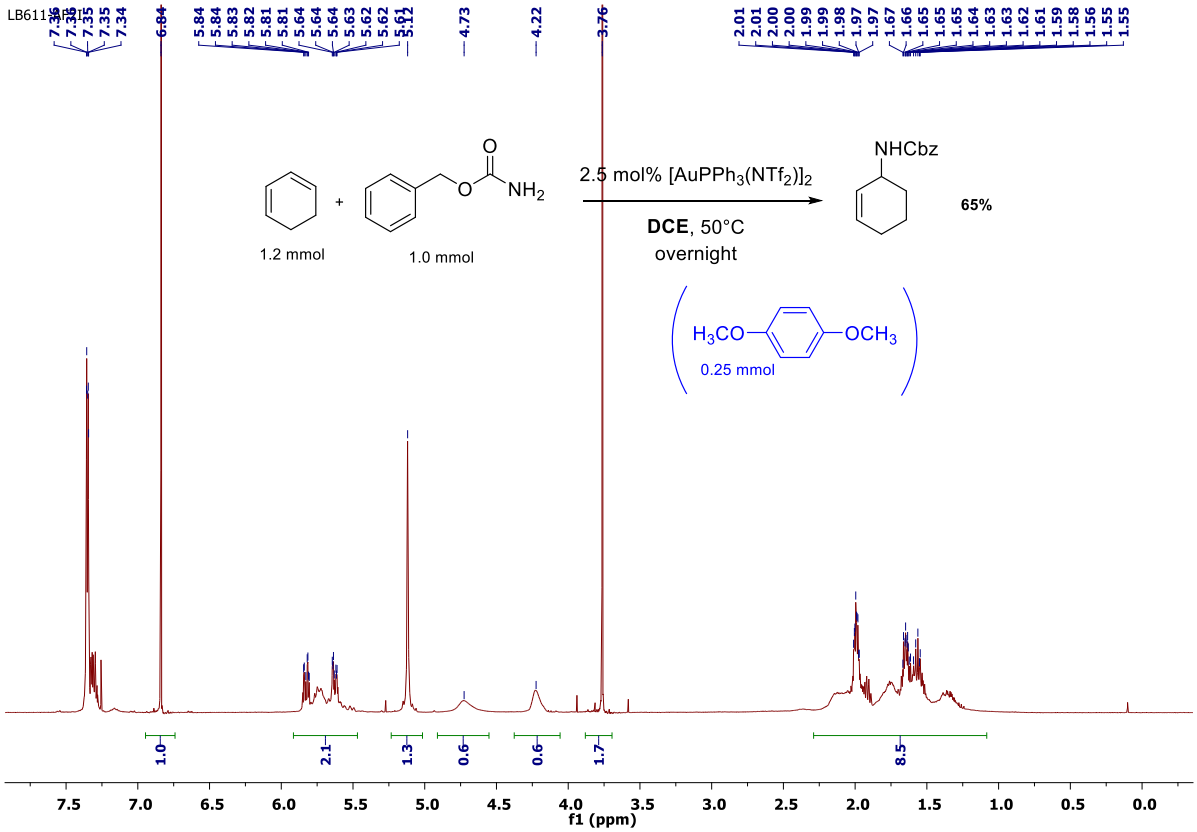
80
70
60
50
40
30
20
10
f1 (ppm)

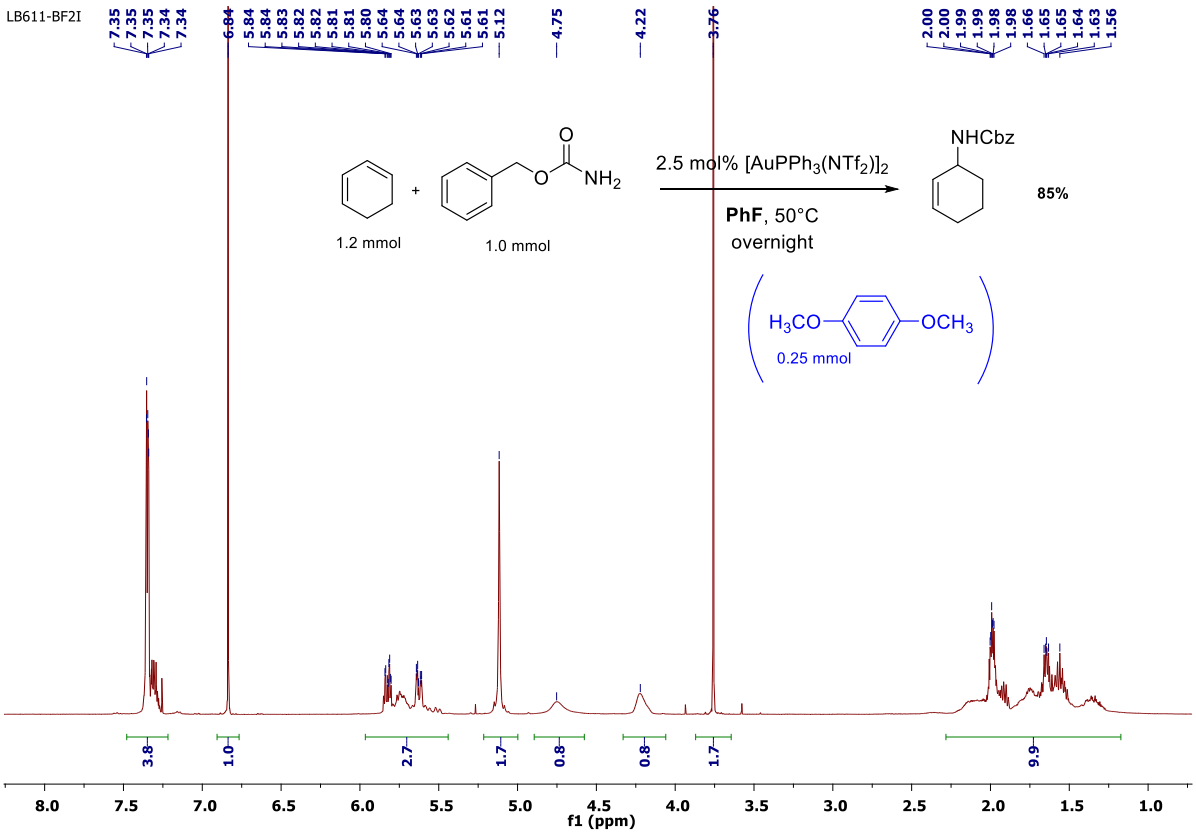
Gold catalysed hydroamination of 1,3-dienes[2]



Entry	Solvent	Yields (%)
A	$ClCH_2CH_2Cl$	65
B	PhF	85
C	$PhCF_3$	65

General procedure: $[Au(PPh_3)(NTf_2)]_2$.PhMe (40 mg, 0.025 mmol) and benzyl carbamate (150 mg, 1.0 mmol) were placed in a Schlenck tube and degassed (3 x vac/Ar cycles) before addition of the solvent (2 mL) and 1,3-cyclohexadiene (120 µL, 1.2 mmol). The resulting mixture was stirred overnight at 50 °C under exclusion of light. The volatiles were removed under vacuum and the crude residue was purified by column chromatography on silica using PEth/EtOAc (100/0 to 80/20). Evaporation of the solvent revealed a mixture of desired product along with 1,3-cyclohexadiene. The yield of hydroamination product was evaluated by ^{1}H NMR using 1,4-dimethoxybenzene (0.25 mmol, 35 mg) as an internal standard. The signals used to quantify the product were the aromatic signal of the internal standard (6.84 ppm, s) and the -CH_2 signal of the benzyl group in the product (5.12 ppm, s).

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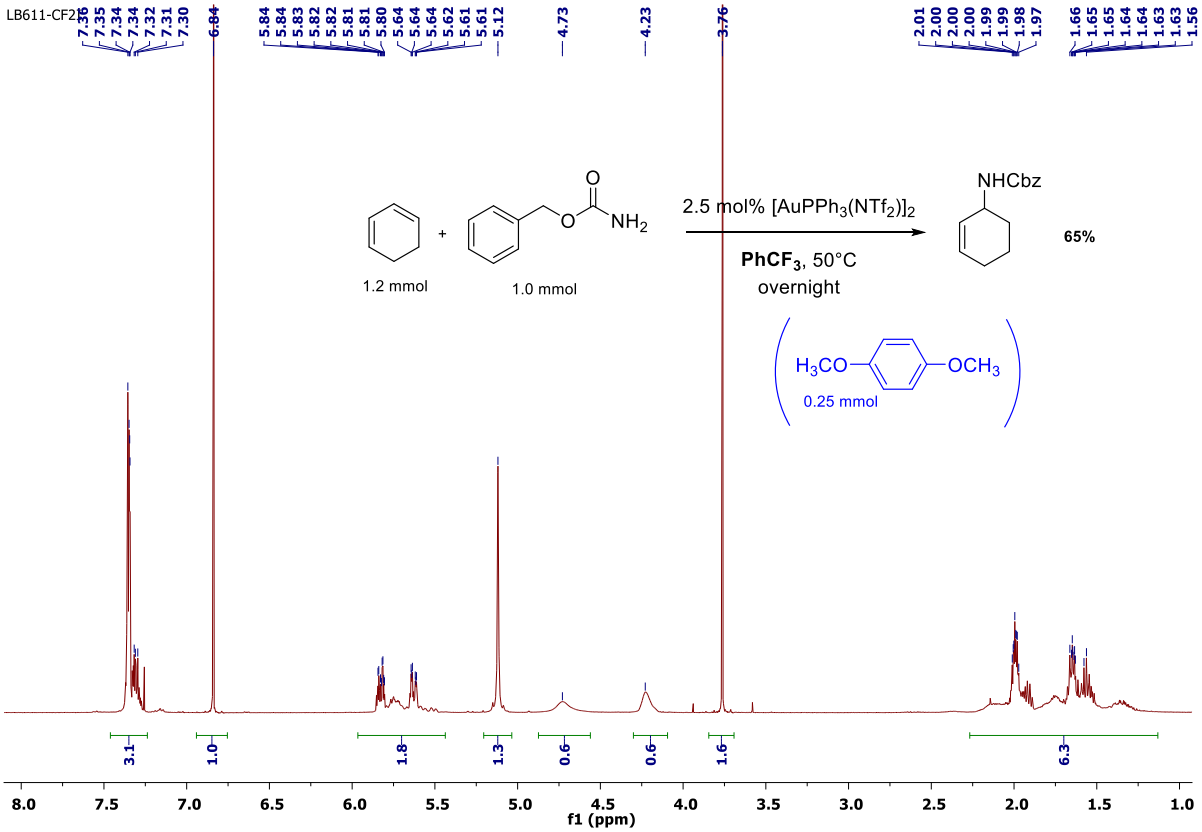
6.84
5.84 5.84 5.83 5.82 5.82 5.81 5.81 5.80 5.64 5.63 5.63 5.62 5.61 5.61 5.12
4.75
4.22
3.76
2.00 2.00 1.99 1.99 1.98 1.98 1.66 1.65 1.65 1.64 1.63 1.56
O
O
NH2
1.2 mmol
1.0 mmol
2.5 mol% [AuPPh3(NTf2)]2
PhF, 50°C
overnight
NHCbz
85%
H3CO
OCH3
0.25 mmol
3.8
1.0
2.7
1.7
0.8
0.8
1.7
9.9
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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6.84
5.84 5.84 5.83 5.82 5.82 5.81 5.81 5.80 5.64 5.64 5.62 5.61 5.61 5.12
4.73
4.23
3.76
2.01 2.00 2.00 2.00 1.99 1.99 1.98 1.97 1.66 1.65 1.65 1.64 1.64 1.63 1.56
O
O
NH2
1.2 mmol
1.0 mmol
2.5 mol% [AuPPh3(NTf2)]2
PhCF3, 50°C
overnight
NHCbz
65%
H3CO
OCH3
0.25 mmol
3.1
1.0
1.8
1.3
0.6
0.6
1.6
6.3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

2. Experimental Procedures, Data and Spectra for SNAr products

Material and Methods

3-Amino-5-methylpyrazole was purchased from Alfa Aesar. All other reagents were purchased from Sigma-Aldrich Co. Ltd. unless otherwise stated, and used without further purification. All reagents were of commercial quality and used as received.

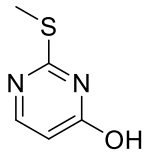
Microwave reactions were performed on a Personal Chemistry Smith Creator Microwave Assisted Organic Synthesizer.

Thin layer chromatography (TLC) was performed on aluminium backed Sigma-Aldrich TLC plates with F_{254} fluorescent indicator. Developed plates were air dried and analysed under a UV light or by staining with the appropriate indicator. Normal phase flash column chromatography was carried out using silica gel (43-60 μm) supplied by Merck.

HRMS refers to high resolution mass spectrometry. Electrospray ionization (ESI) accurate mass was determined using Waters LCT Premier XE instrumentation. Infrared spectra were recorded using a Perkin Elmer 100 FT-IR spectrometer and adsorption maxima are reported in wavenumbers (cm^{-1}). Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected.

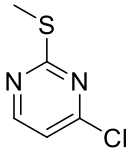
NMR (^{1}H and ^{13}C) was performed on a 600 MHz AMX Bruker Spectrometer. The chemical shifts (δ) are given in units of ppm relative to tetramethylsilane (TMS), where δ(TMS) = 0 ppm. Data processing was carried out using the TOPSPIN 2 NMR program (Bruker UK Ltd). For ^{1}H NMR, the multiplicity used for assignment is indicated by the following abbreviations: s = singlet, d = doublet, m = multiplet, br = broad and the coupling constants (*J*) were measured in Hertz (Hz). ^{13}C NMR have been assigned using DEPT, HSQC and HMBC NMR as performed on 600 MHz AMX Bruker Spectrometers. Deuterated chloroform ($CDCl_3$), dimethylsulfoxide (d_6-DMSO) and methanol (CD_3OD) were used as solvents (as stated) for all NMR analysis.

2-(Methylthio)pyrimidin-4-ol[3]



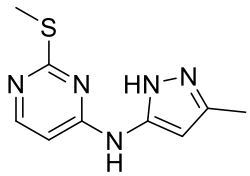
2-Thiouracil (10.00 g, 78.0 mmol) was added to a solution of sodium hydroxide (6.24 g, 156 mmol) in H_2O (0.7 mL per mmol). The reaction was cooled to 0 °C in an ice bath before methyl iodide (7.30 mL, 117 mmol) was added dropwise and the reaction stirred at RT for 16 h. The reaction mixture was cooled in an ice bath before acidifying with glacial acetic acid. A precipitate appeared which was filtered, washed with H_2O and dried to give the phenol (8.32 g, 75%) as an off-white solid; R_f 0.45 (5% MeOH/CH_2Cl_2); mp 162 - 164 °C (lit. 99 - 101 °C[3]); ^{1}H NMR (600 MHz, d_6-DMSO) δ 12.68 (1H, br, OH), 7.86 (1H, d, J = 4.0 Hz, H6), 6.09 (1H, d, J = 4.0 Hz, H5) and 2.47 (3H, s, CH_3); ^{13}C NMR (150 MHz, d_6 - DMSO) δ 163.4 (C2), 162.9 (C4), 153.7 (C6), 109.9 (C5) and 12.9 (CH_3); LRMS (ES+) 142.9 $[M+H]^+$. The data is in good agreement with the literature values.[3]

4-Chloro-2-(methylthio)pyrimidine (**11**)



2-(Methylthio)pyrimidin-4-ol (7.00 g, 49.3 mmol) was added to $POCl_3$ (0.6 mL per mmol) under argon and the mixture heated at 80 °C for 5 h. The reaction was cooled to RT and quenched by carefully adding to warm H_2O (500 mL) before being extracted with CH_2Cl_2 (3 × 500 mL). The organic layer was washed with 10% K_2CO_3 solution (750 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **11** (5.70 g, 70%) as a colourless oil; R_f 0.71 (5% MeOH/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (1H, d, J = 5.1 Hz, H6), 6.99 (1H, d, J = 5.1 Hz, H5) and 2.55 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1 (C2), 161.1 (C4), 158.1 (C6), 116.5 (C5) and 14.4 (CH_3); LRMS (ES+) 160.9 $[M+H]^+$. The data is in good agreement with the literature values.[4]

***N*-(3-Methyl-1H-pyrazol-5-yl)-2-(methylthio)pyrimidin-4-amine** (**13a**)



Method 1 (thermal reaction before optimisation):[4]

N,*N*-Diisopropylethylamine (DIPEA) (5.23 mL, 30.0 mmol) and sodium iodide (4.50 g, 30.0 mmol) were added to a solution of aryl chloride **11** (4.00 g, 25.0 mmol) and 3-amino-5-methylpyrazole **12** (2.45 g, 25.0 mmol) in DMF (3 mL per mmol). The reaction was heated at 85 °C for 89 h. The

reaction mixture was cooled to RT before diluting with EtOAc (250 mL) and washing with H_2O (3 × 250 mL). The combined aqueous layers were extracted with EtOAc (2 × 250 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10 – 75% EtOAc/Pet. Ether) gave **13a** (995 mg, 18% yield) as an off-white solid.

Method 2 (microwave conditions before optimisation):

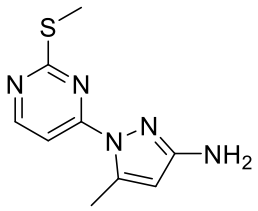
A mixture of aryl chloride **11** (100 mg, 0.63 mmol), 3-amino-5-methylpyrazole **12** (61.7 mg, 0.63 mmol), DIPEA (132 µL, 0.76 mmmol) and sodium iodide (114 mg, 0.76 mmol) in DMF (3 mL per mmol) was heated in a microwave at 180 ºC for 2 h. The reaction mixture was cooled to RT before diluting with EtOAc (10 mL) and washing with H_2O (3 × 10 mL). The combined aqueous layers were extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10 – 75% EtOAc/Pet. Ether) gave **13a** (26.6 mg, 19% yield) as an off-white solid.

Method 3 (microwave conditions after optimisation):

A solution of aryl chloride **11** (400 mg, 2.50 mmol) and 3-amino-5-methylpyrazole **12** (485 mg, 5.00 mmol) in dipropyl ether (5 mL) was heated in a microwave at 140 ºC for 2 h. The reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (10 – 75% EtOAc/Pet. Ether) gave **13a** (314 mg, 57%) as an off-white solid.

R_f 0.25 (80% EtOAc/Pet. Ether); mp 207 – 210 ºC; IR ν_{max} (solid) 3280 (NH), 3160 (NH), 3100 - 2920 (CH) cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.98 (1H, d, *J* = 5.6 Hz, H6); 6.69 (1H, br, H5), 6.23 (1H, br, H13), 2.52 (3H, s, H8) and 2.28 (3H, s, H15); ^{13}C NMR (150 MHz, CD_3OD) δ 172.9 (C2), 161.4 (C4), 156.1 (C6), 149.4 (Pyrazole C3), 141.3 (Pyrazole C5), 102.4 (C5), 97.7 (Pyrazole C4), 14.1 (CH_3) and 10.9 (CH_3); HRMS calc. for $C_9H_{12}N_5S$ expected 222.0813; found 222.0802.

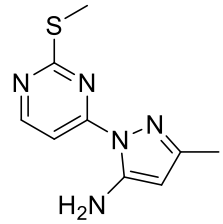
5-Methyl-1-(2-(methylthio)pyrimidin-4-yl)-1H-pyrazol-3-amine (13b)



R_f 0.65 (80% EtOAc/Pet. Ether); mp 116-119 ºC; IR ν_{max} (solid) 3260 (NH_2), 2990 - 2900 (CH) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.44 (1H, d, *J* = 5.7 Hz, H6), 7.50 (1H, d, *J* = 5.7 Hz, H5), 5.84 (2H, br, NH_2), 5.33 (1H, s, H12), 2.57 (3H, s, H8) and 2.20 (3H, s, H14); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4 (C2), 159.6 (C4), 158.1 (C6), 153.6 (Pyrazole C5), 150.1 (Pyrazole C3), 104.7 (C4), 90.5

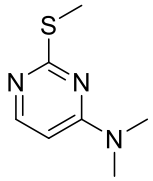
(Pyrazole C4), 14.3 (CH_3) and 14.1 (CH_3); HRMS calc. for $C_9H_{12}N_5S$ expected 222.0813; found 222.0815.

3-Methyl-1-(2-(methylthio)pyrimidin-4-yl)-1H-pyrazole-5-amine (13c)



R_f 0.55 (80% EtOAc/Pet. Ether); mp 102-103 ºC; IR ν_{max} (solid) 3350 (NH_2), 2990 - 2920 (CH) cm^{-1}; ^1H NMR (600 MHz, d_6-DMSO) δ 8.43 (1H, d, *J* = 5.6 Hz, H6), 7.27 (1H, d, *J* = 5.6 Hz, H5), 5.72 (1H, s, H12), 5.44 (2H, br, NH_2) and 2.63 (3H, s, H15). H8 signal under DMSO solvent peak.^{13}C NMR (150 MHz, d_6-DMSO) δ 170.8 (C2), 158.2 (C6), 157.4 (C4), 157.3 (Pyrazole C3), 142.7 (Pyrazole C5), 104.3 (C5), 101.8 (Pyrazole C4), 15.9 (CH_3) and 13.8 (CH_3); LRMS (ES+) 222.2 $[M+H]^+$; HRMS calc. for $C_9H_{12}N_5S$ expected 222.0813; found 222.0810.

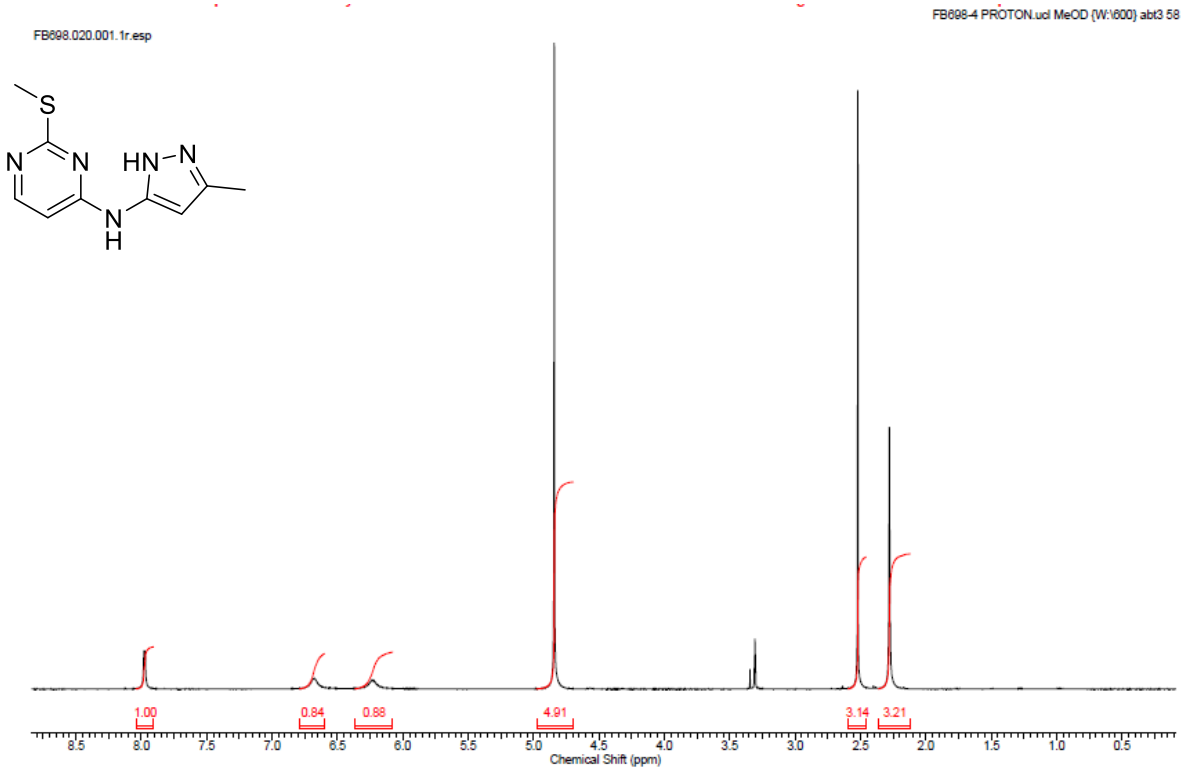
2-(Methylthio)pyrimidin-4-amine (13d)



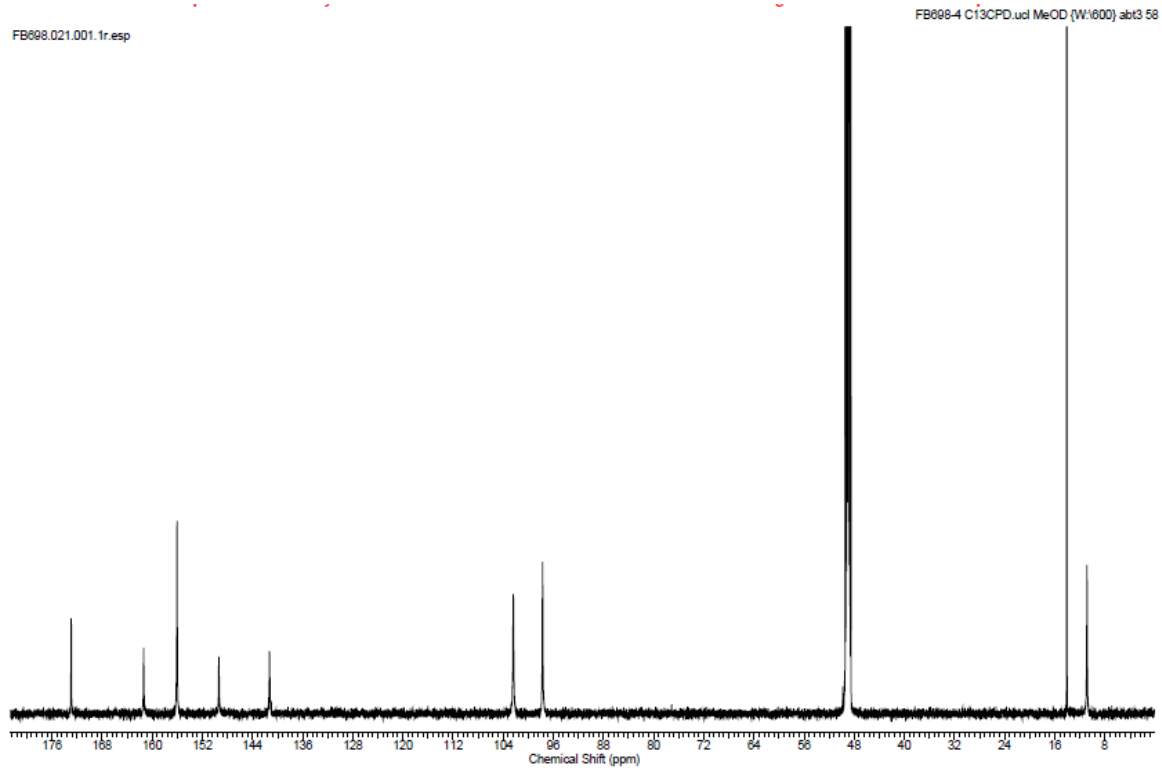
R_f 0.70 (80% EtOAc/Pet. Ether); IR ν_{max} (oil) 3010 - 2920 (CH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 6.0 Hz, H6), 6.11 (1H, d, *J* = 6.0 Hz, H5), 3.10 (6H, br, H10) and 2.51 (3H, s, H8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (C2), 161.5 (C4), 155.3 (C6), 98.3 (C5), 37.0 (NCH_3) and 14.2 (CH_3); HRMS calc. for $C_7H_{12}N_3S$ expected 170.0752; found 170.0755.

N-(3-Methyl-1H-pyrazol-5-yl)-2-(methylthio)pyrimidin-4-amine (13a)

^{1}H NMR

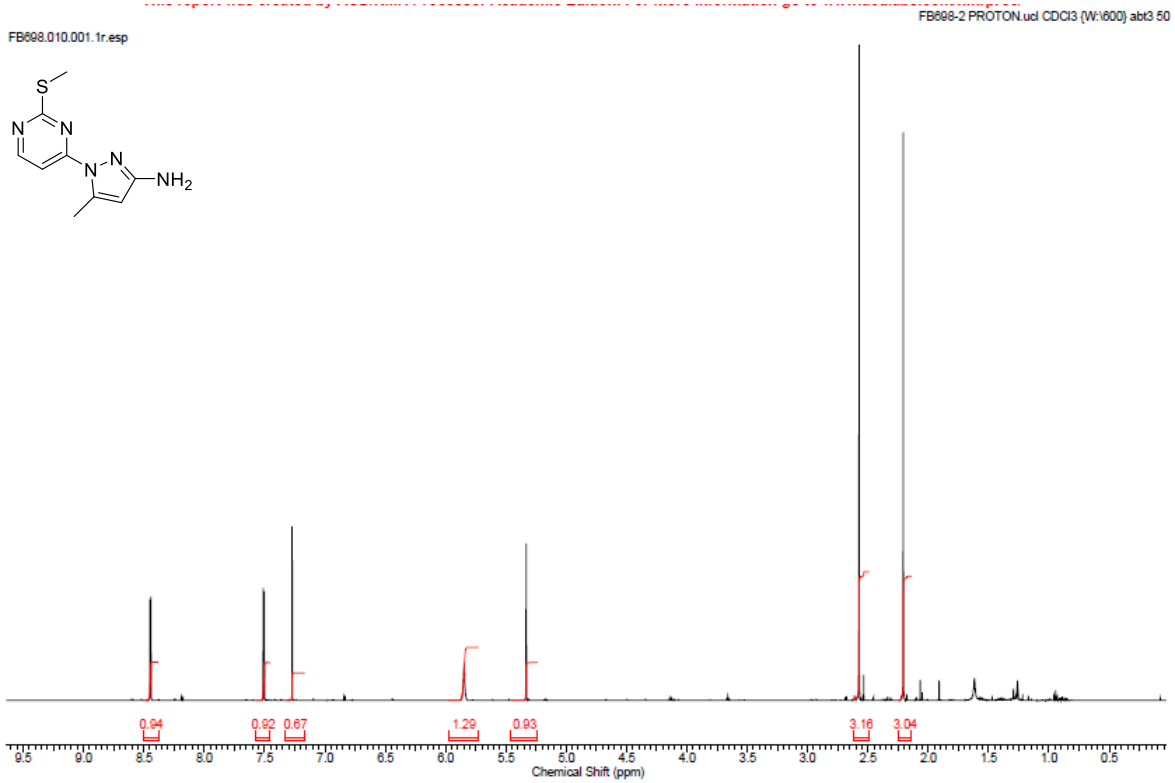


^{13}C NMR

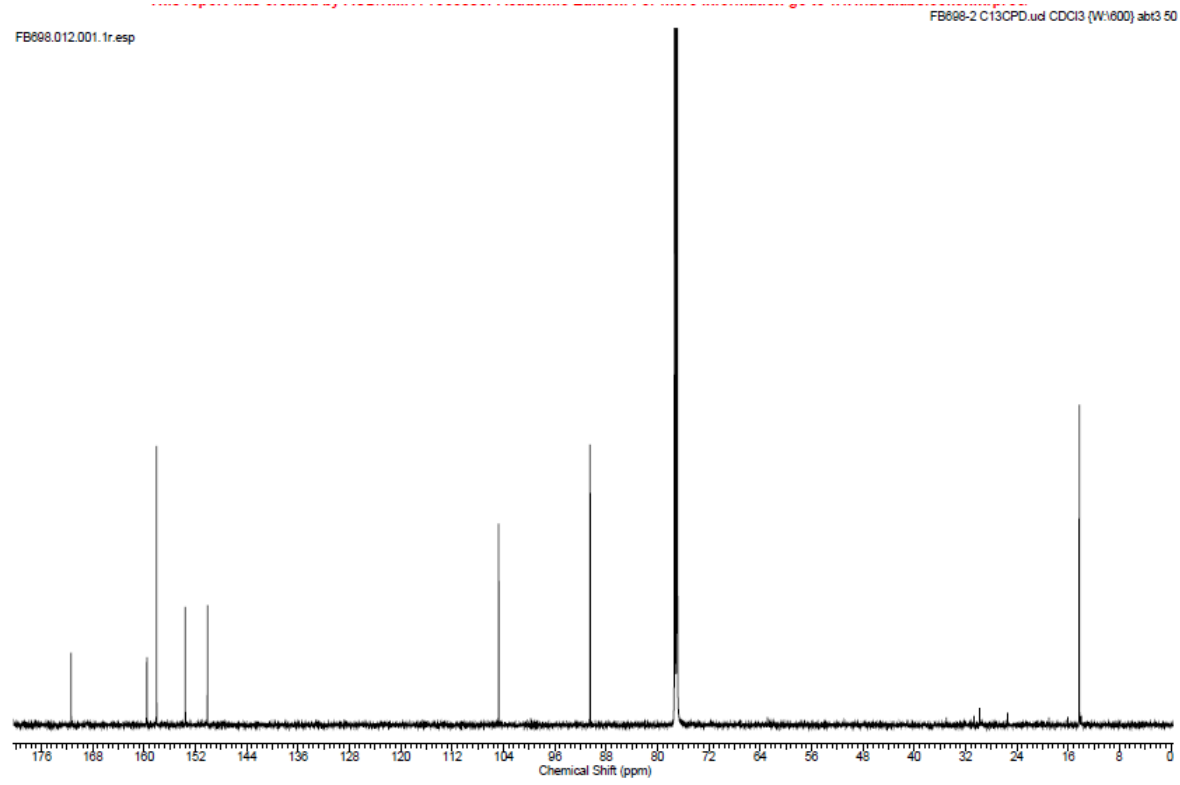


5-Methyl-1-(2-(methylthio)pyrimidin-4-yl)-1H-pyrazol-3-amine (13b)

^{1}H NMR

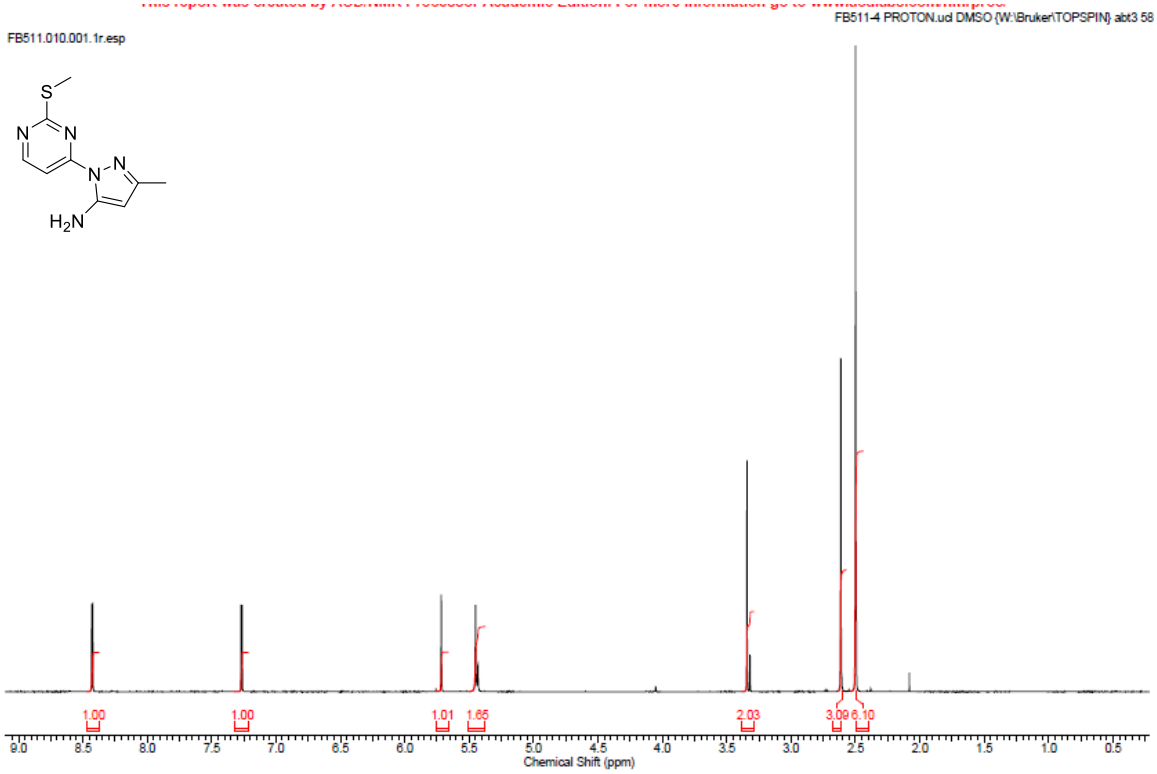


^{13}C NMR

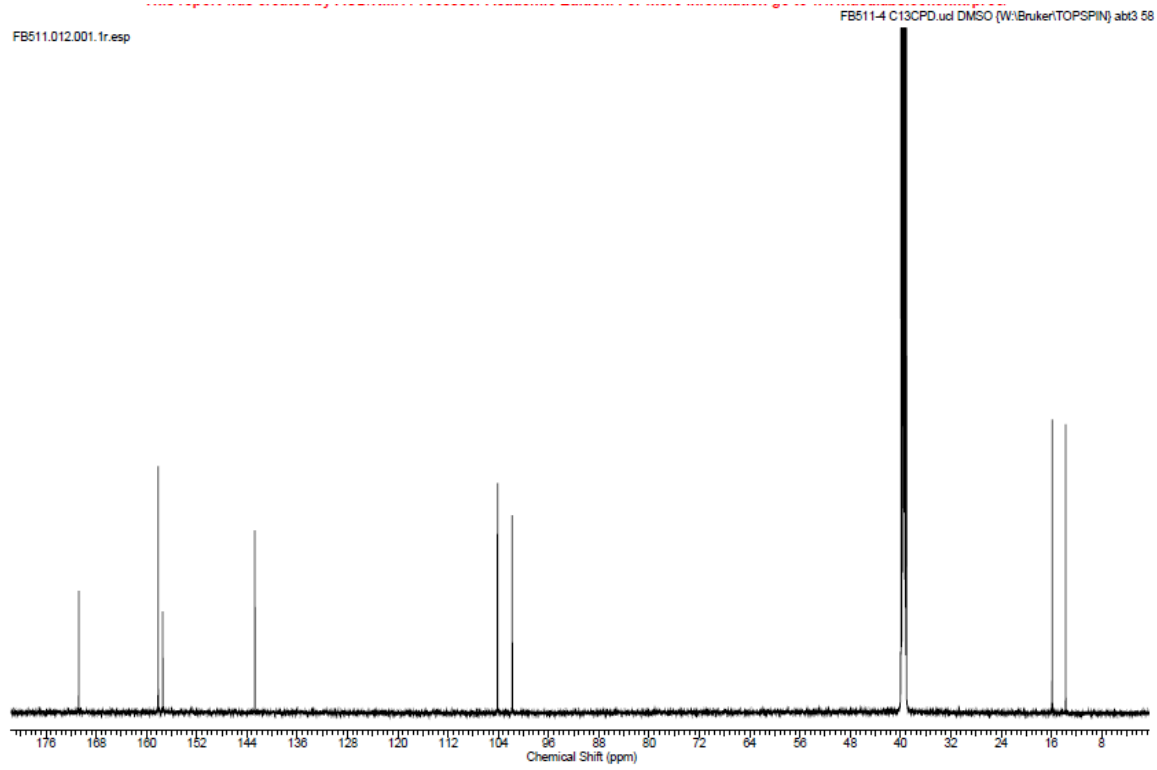


3-Methyl-1-(2-(methylthio)pyrimidin-4-yl)-1H-pyrazole-5-amine (13c)

^{1}H NMR

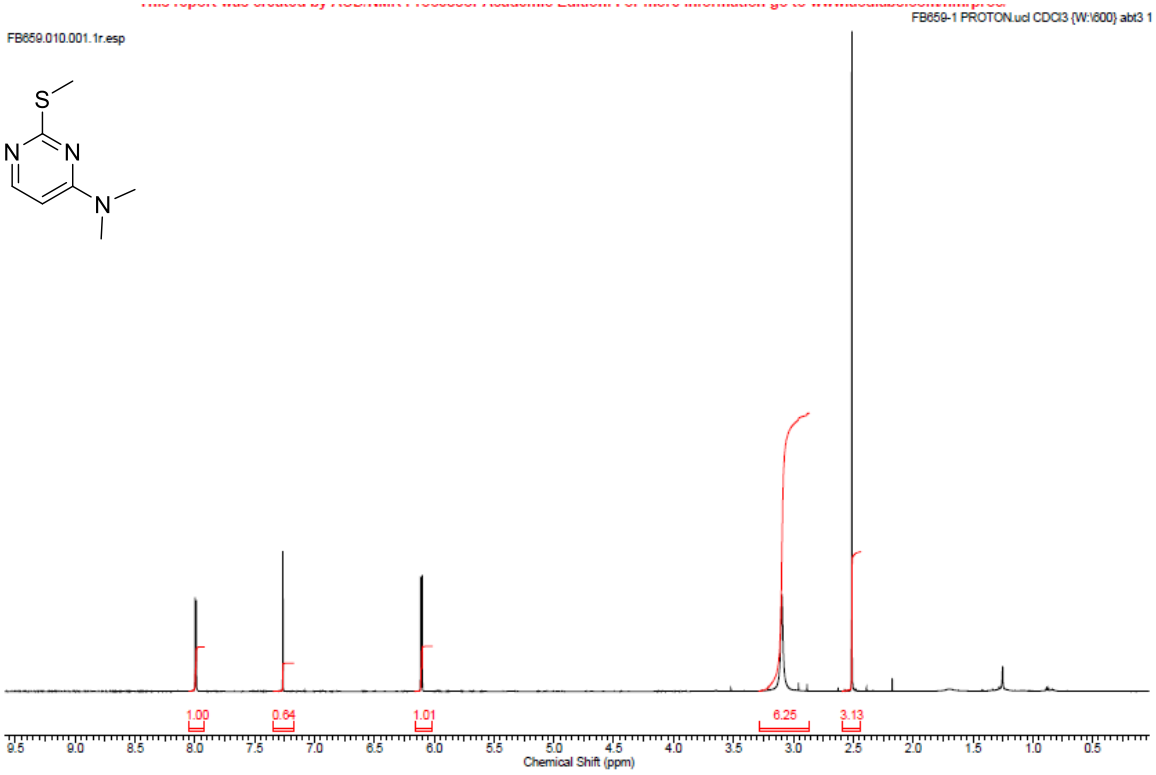


^{13}C NMR

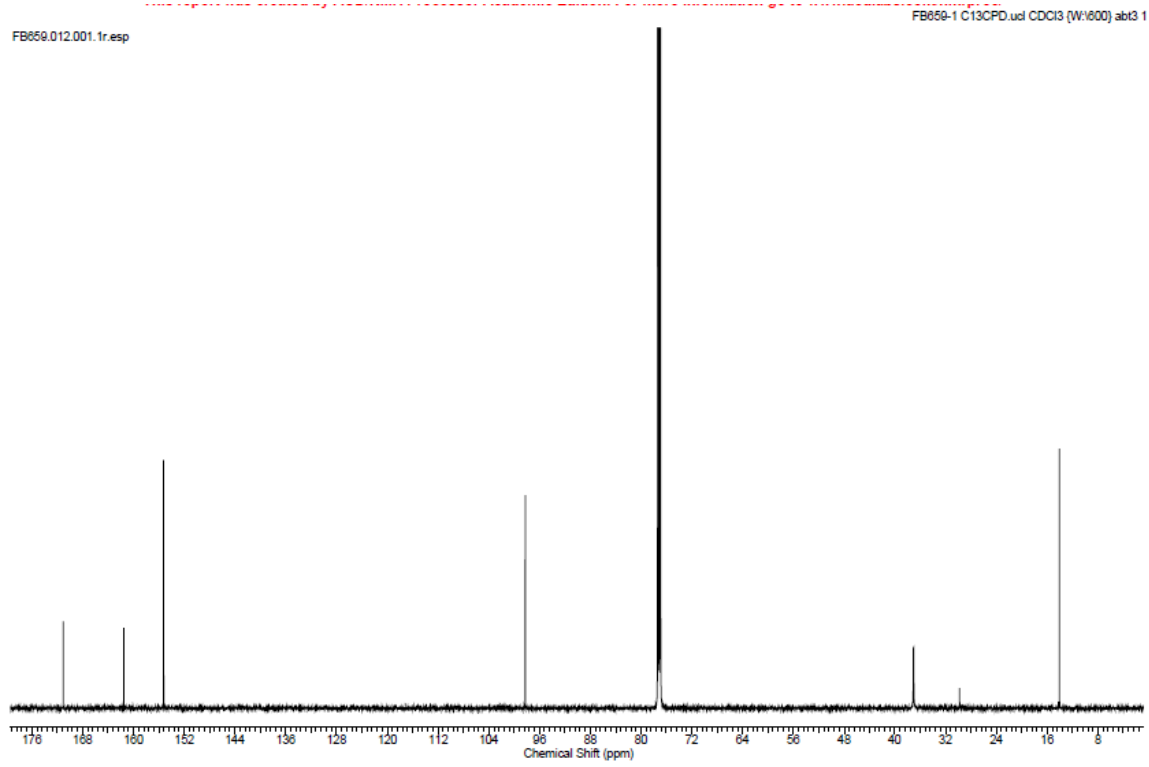


2-(Methylthio)pyrimidin-4-amine (13d)

^{1}H NMR

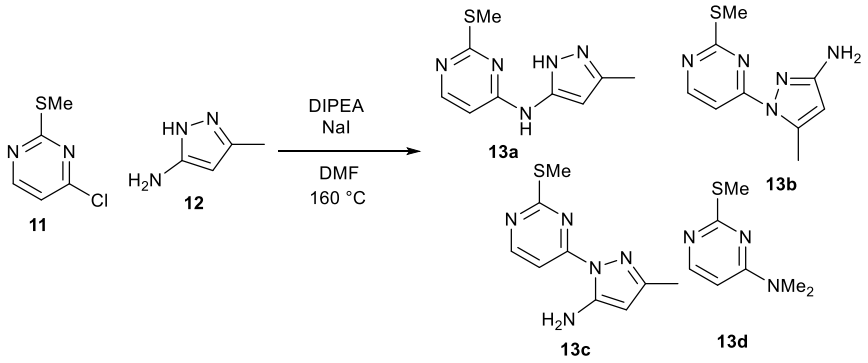


^{13}C NMR



3. Design of Experiments Optimisation of S_NAr reaction

a. Optimisation of the S_NAr reaction in DMF



The experimental design was produced using MODDE 10 software as a Resolution V design consisting of 16 experiments plus three centre points as shown below. The yields of all four reaction products **13a-13d**, as well as the quantity of recovered starting material, were determined by ^1H NMR.

Run Order	Amine eq	NaI eq	DIPEA Eq	DMF vol	Temp
1	1.25	1.05	3	3.5	160
2	0.5	2	1	2	120
3	0.5	2	5	5	120
4	0.5	0.1	1	5	120
5	2	2	1	5	120
6	0.5	0.1	5	5	200
7	2	0.1	1	5	200
8	2	2	5	2	120
9	0.5	2	1	5	200
10	2	2	5	5	200
11	2	0.1	5	2	200
12	0.5	2	5	2	200
13	1.25	1.05	3	3.5	160
14	0.5	0.1	1	2	200
15	2	0.1	5	5	120
16	0.5	0.1	5	2	120
17	1.25	1.05	3	3.5	160
18	2	2	1	2	200
19	2	0.1	1	2	120

Experimental Procedure and Analysis Method

Stock solutions of aryl chloride **11** (1.26 M) and 3-amino-5-methylpyrazole **12** (1.87 M**)** in DMF and 1,3,5-trimethoxybenzene (0.092 M) in CD_3OD were prepared.

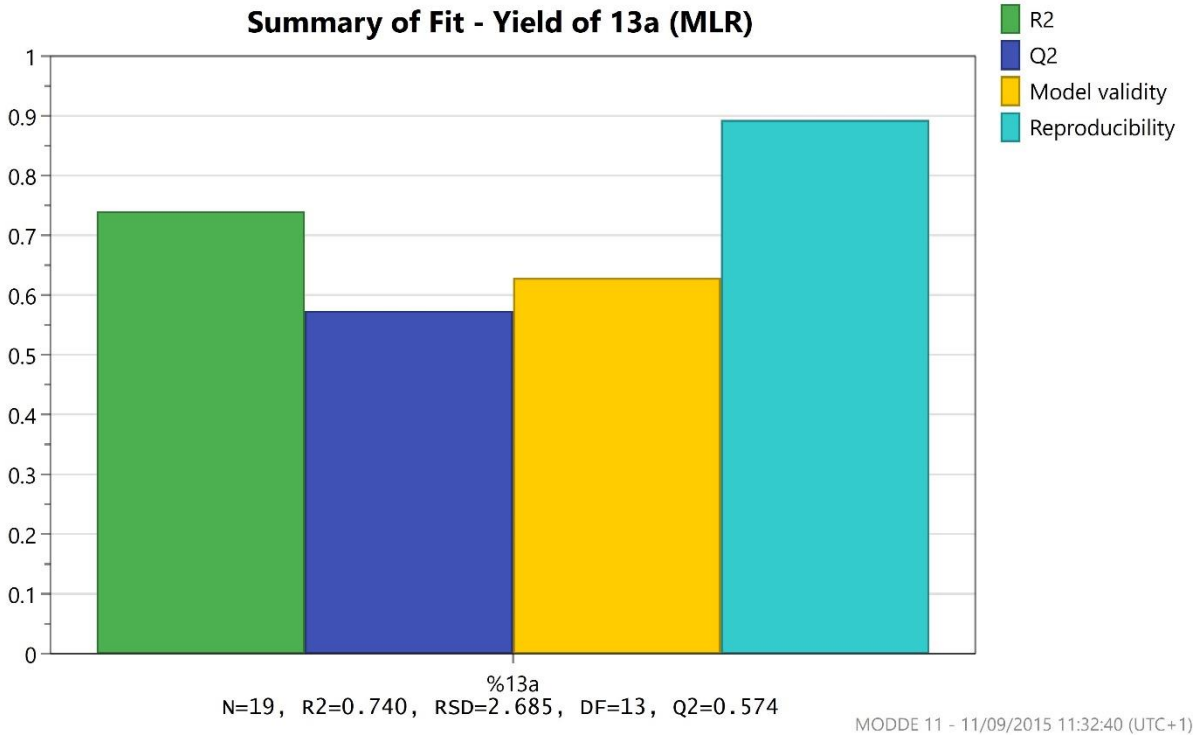
A mixture of aryl chloride **11** (1.26 M in DMF, 500 µL, 0.63 mmol), 3-amino-5-methylpyrazole **12** (1.87 M in DMF, 0.17-0.42 mL), DIPEA (1-3 eq) and sodium iodide (9-189 mg) and DMF (volume shown in table below) was heated in the microwave at the stated temperature for 2 h. The reaction mixture was cooled to RT before concentrating *in vacuo*. The crude reaction residue was dissolved in CD_3OD (1 mL) and an aliquot (200 µL) removed. For NMR analysis, the reaction mixture aliquot was mixed with 1,3,5-trimethoxybenzene solution (0.092 M in CD_3OD, 500 µL).

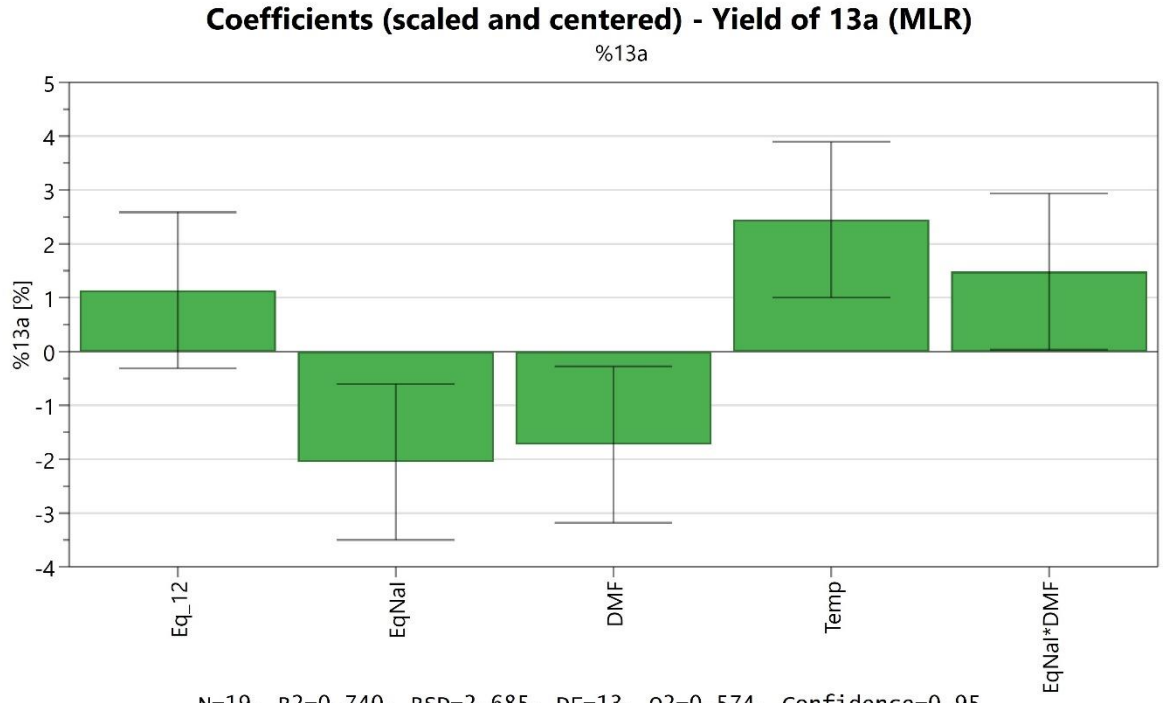
Conditions and quantities for each reaction are shown in the table below.

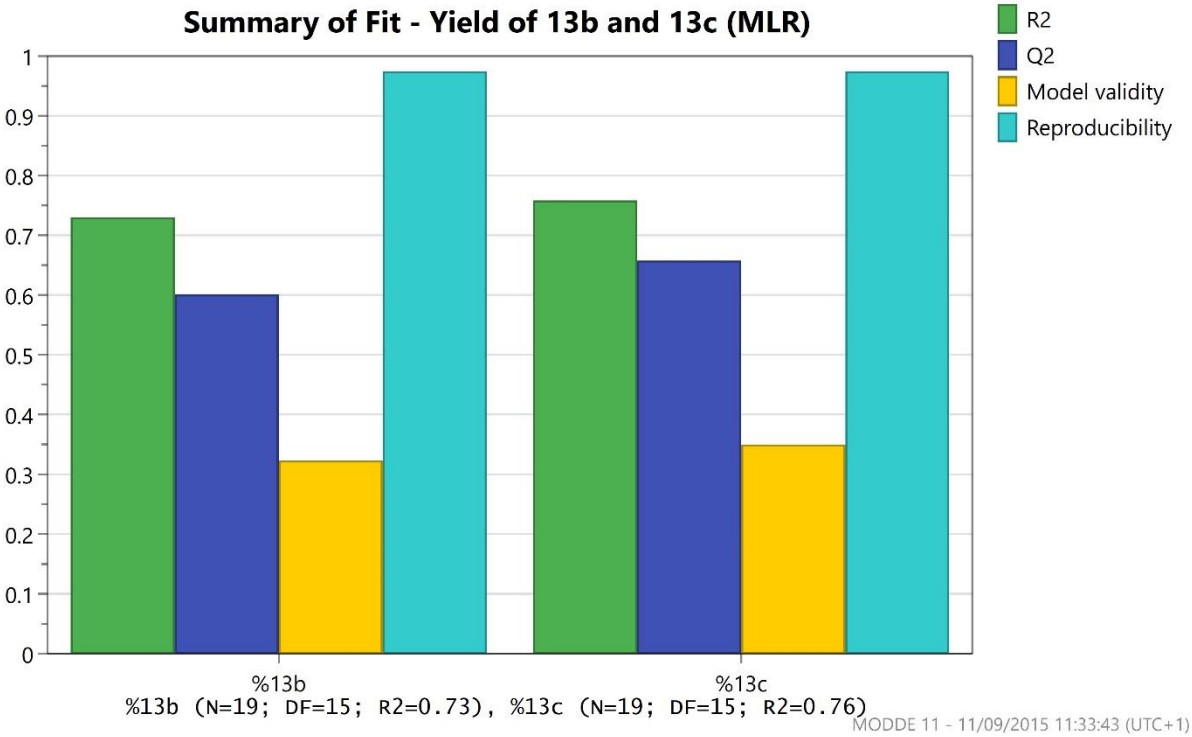
Run Order	12 (eq)	12 (mL)	NaI (eq)	NaI (mmol)	NaI (mg)	DIPEA (eq)	DIPEA (mL)	Total DMF (mL)	DMF (mL)	Temp (°C)
1	1.25	0.42	1.05	0.66	99	3	0.33	3.5	2.58	160
2	0.5	0.17	2	1.26	189	1	0.11	2	1.33	120
3	0.5	0.17	2	1.26	189	5	0.55	5	4.33	120
4	0.5	0.17	0.1	0.06	9	1	0.11	5	4.33	120
5	2	0.67	2	1.26	189	1	0.11	5	3.83	120
6	0.5	0.17	0.1	0.06	9	5	0.55	5	4.33	200
7	2	0.67	0.1	0.06	9	1	0.11	5	3.83	200
8	2	0.67	2	1.26	189	5	0.55	2	0.83	120
9	0.5	0.17	2	1.26	189	1	0.11	5	4.33	200
10	2	0.67	2	1.26	189	5	0.55	5	3.83	200
11	2	0.67	0.1	0.06	9	5	0.55	2	0.83	200
12	0.5	0.17	2	1.26	189	5	0.55	2	1.33	200
13	1.25	0.42	1.05	0.66	99	3	0.33	3.5	2.58	160
14	0.5	0.17	0.1	0.06	9	1	0.11	2	1.33	200
15	2	0.67	0.1	0.06	9	5	0.55	5	3.83	120
16	0.5	0.17	0.1	0.06	9	5	0.55	2	1.33	120
17	1.25	0.42	1.05	0.66	99	3	0.33	3.5	2.58	160
18	2	0.67	2	1.26	189	1	0.11	2	0.83	200
19	2	0.67	0.1	0.06	9	1	0.11	2	0.83	120

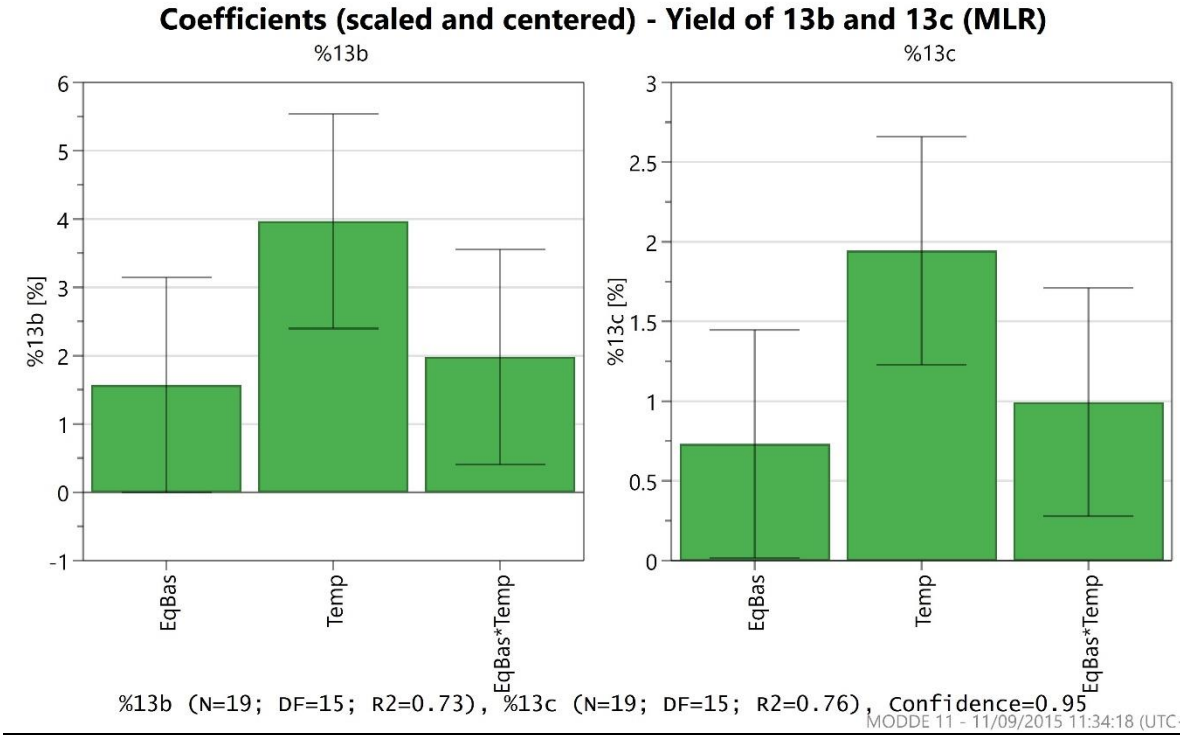
Results of the First DoE Experiments

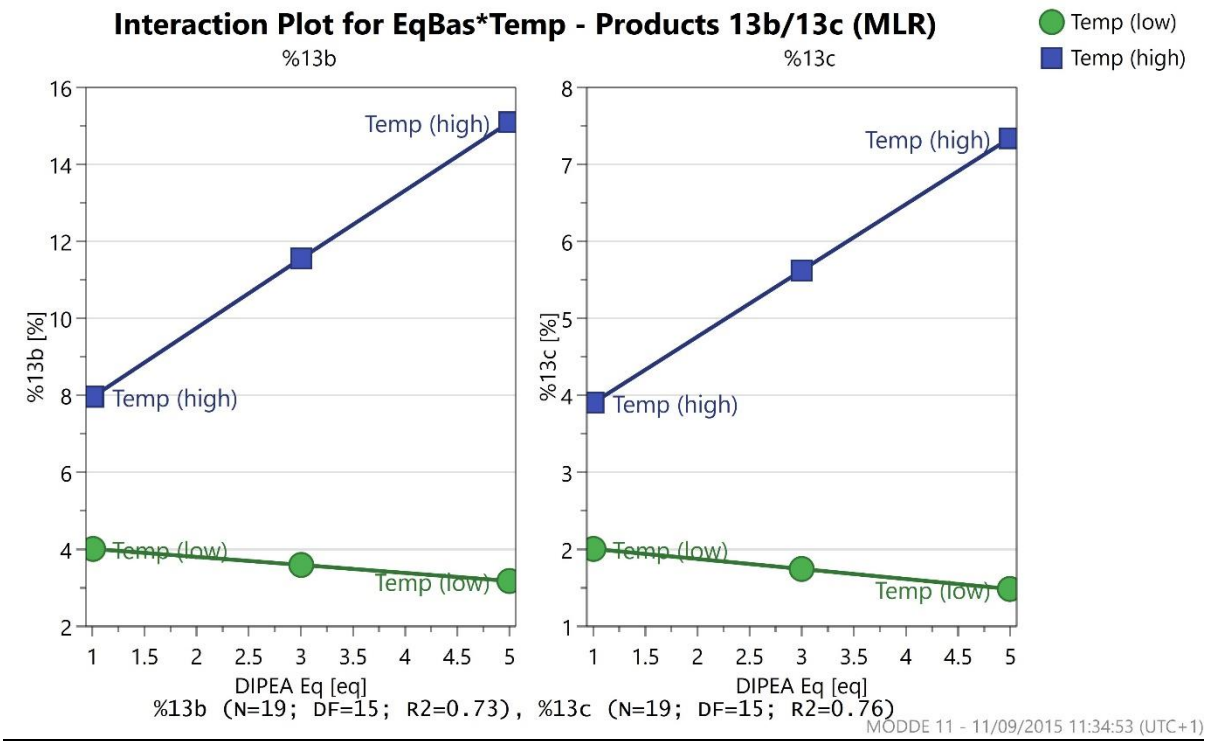
Run Order	Incl/Excl	Amine eq	NaI eq	DIPEA Eq	DMF vol	Temp	%A	%B	%C	%D	%SM
1	Incl	1.25	1.05	3	3.5	160	15.3	12.4	6.2	16.4	9.5
2	Incl	0.5	2	1	2	120	4	1.9	1	0.9	46.3
3	Incl	0.5	2	5	5	120	3.1	1.1	0.5	1.8	18.6
4	Incl	0.5	0.1	1	5	120	4.7	1.8	0.7	1.4	40.1
5	Incl	2	2	1	5	120	8	3	1.6	2.8	22
6	Incl	0.5	0.1	5	5	200	11.6	14.2	6.3	54.3	0
7	Incl	2	0.1	1	5	200	11.3	8.8	4.3	59.8	0
8	Incl	2	2	5	2	120	6.8	3.7	1.8	2.2	21.2
9	Incl	0.5	2	1	5	200	9.1	5.8	2.9	38.3	0
10	Incl	2	2	5	5	200	10.9	13.5	6.9	31	0
11	Incl	2	0.1	5	2	200	16.4	18.6	8.8	43	0
12	Incl	0.5	2	5	2	200	10.2	10.9	5.8	25.6	0
13	Incl	1.25	1.05	3	3.5	160	16.4	12	5.8	13.9	12
14	Incl	0.5	0.1	1	2	200	18.6	9.9	3.7	60.6	0
15	Incl	2	0.1	5	5	120	8	2.9	1.1	3.3	34.3
16	Incl	0.5	0.1	5	2	120	10.1	1.9	0.9	2	28.3
17	Incl	1.25	1.05	3	3.5	160	13.5	10.8	5.4	18.6	6.7
18	Incl	2	2	1	2	200	12	4.3	3.1	30.5	0
19	Incl	2	0.1	1	2	120	16.2	6.2	3.1	9.7	14.7

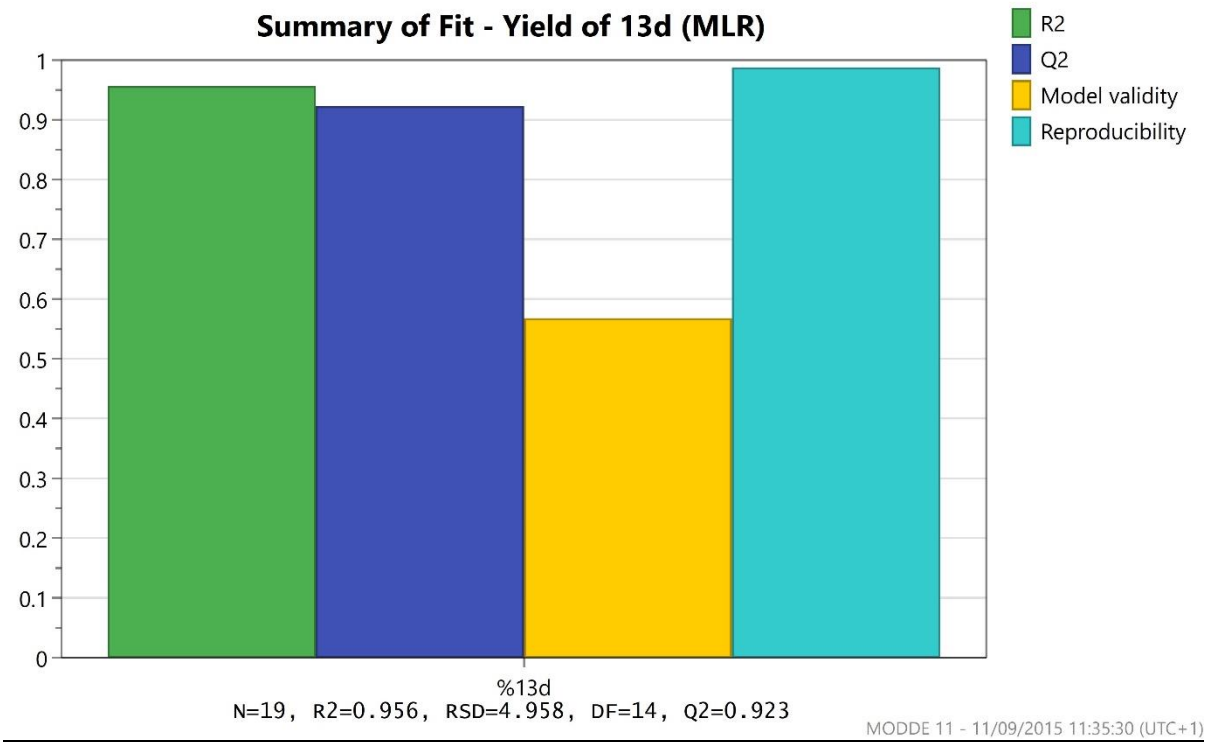


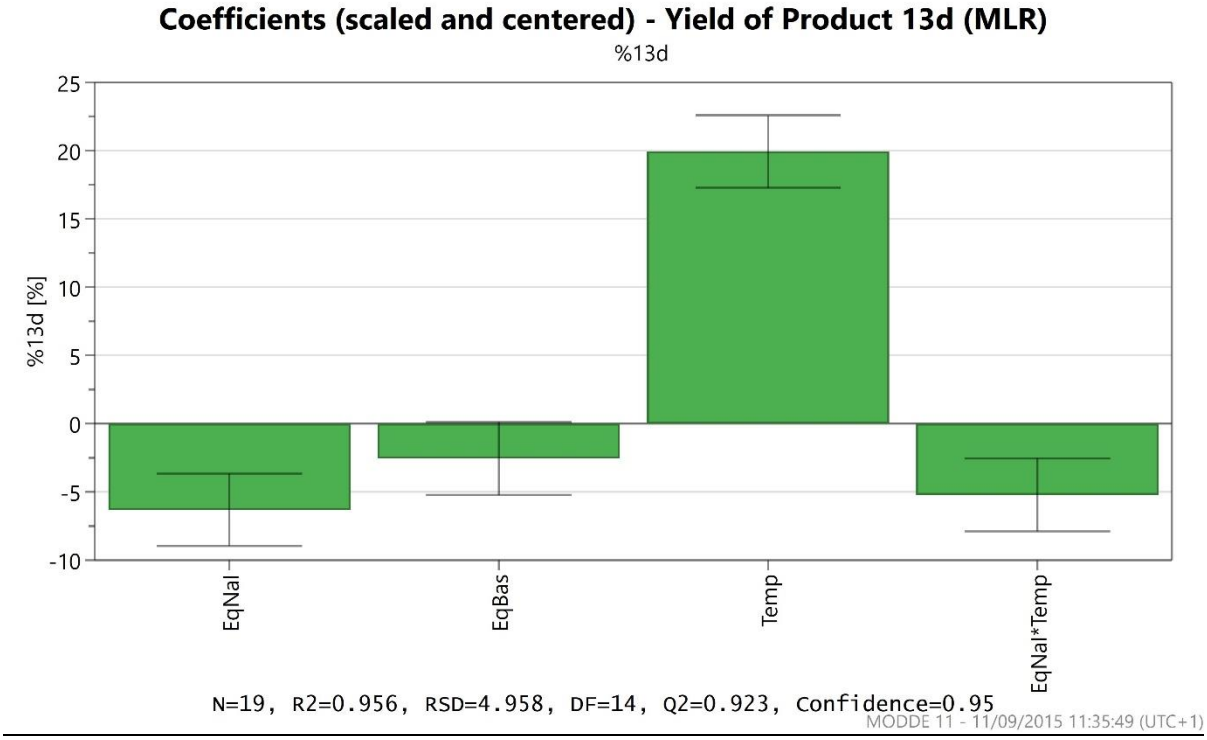

Coefficients (scaled and centered) - Yield of 13a (MLR)
%13a
%13a [%]
5
4
3
2
1
0
-1
-2
-3
-4
Eq_12
EqNaI
DMF
Temp
EqNaI*DMF
N=19, R2=0.740, RSD=2.685, DF=13, Q2=0.574, Confidence=0.95
MODDE 11 - 11/09/2015 11:33:07 (UTC+1)


Summary of Fit - Yield of 13b and 13c (MLR)
R2
Q2
Model validity
Reproducibility
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
%13b
%13c
%13b (N=19; DF=15; R2=0.73), %13c (N=19; DF=15; R2=0.76)
MODDE 11 - 11/09/2015 11:33:43 (UTC+1)

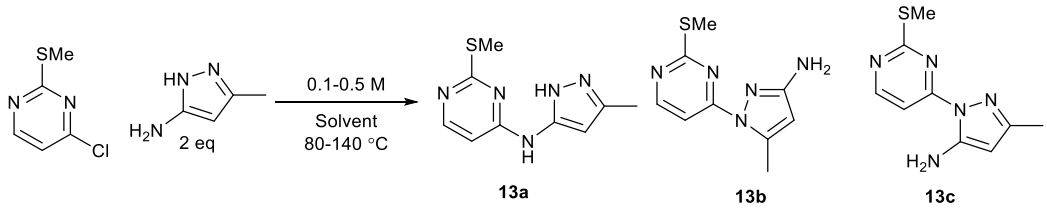

Coefficients (scaled and centered) - Yield of 13b and 13c (MLR)
%13b
%13c
%13b [%]
%13c [%]
EqBas
Temp
EqBas*Temp
%13b (N=19; DF=15; R2=0.73), %13c (N=19; DF=15; R2=0.76), Confidence=0.95
MODDE 11 - 11/09/2015 11:34:18 (UTC+1)


Interaction Plot for EqBas*Temp - Products 13b/13c (MLR)
Temp (low)
Temp (high)
%13b
%13c
%13b [%]
%13c [%]
Temp (high)
Temp (low)
DIPEA Eq [eq]
%13b (N=19; DF=15; R2=0.73), %13c (N=19; DF=15; R2=0.76)
MODDE 11 - 11/09/2015 11:34:53 (UTC+1)


Summary of Fit - Yield of 13d (MLR)
R2
Q2
Model validity
Reproducibility
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
%13d
N=19, R2=0.956, RSD=4.958, DF=14, Q2=0.923
MODDE 11 - 11/09/2015 11:35:30 (UTC+1)


Coefficients (scaled and centered) - Yield of Product 13d (MLR)
%13d
%13d [%]
25
20
15
10
5
0
-5
-10
EqNaI
EqBas
Temp
EqNaI*Temp
N=19, R2=0.956, RSD=4.958, DF=14, Q2=0.923, Confidence=0.95
MODDE 11 - 11/09/2015 11:35:49 (UTC+1)

b. Optimisation of the S_NAr reaction by variation of solvent, temperature and concentration



The experimental design was produced using MODDE 10 software as a Resolution IV design consisting of 8 experiments plus three centre points as shown below. The yields of all three reaction products **13a-13c**, as well as the quantity of recovered starting material, were determined by ^{1}H NMR. The factors investigated were the first two solvent principle components (t1 and t2; -1 to +1 in each case), the temperature (100 to 140 °C) and the concentration (0.1 to 0.5 M)

Run Order	t1	t2	Temp.	Conc.
1	0	0	120	0.3
2	1	1	140	0.1
3	1	-1	140	0.5
4	-1	-1	140	0.1
5	-1	-1	100	0.5
6	1	-1	100	0.1
7	-1	1	140	0.5
8	1	1	100	0.5
9	0	0	120	0.3
10	0	0	120	0.3
11	-1	1	100	0.1

The solvents used for each corner of the design and the centre point are shown below:

	t1=-1		**t1=+1**
t2=+1	**DMA**	**EtCN**	**CPME**
t2=-1	**1-BuOH**		**Pr_2O**

Experimental Procedure and Analysis Method

A Stock solution of 1,3,5-trimethoxybenzene (0.28 M**)** in CH_3OH was prepared.

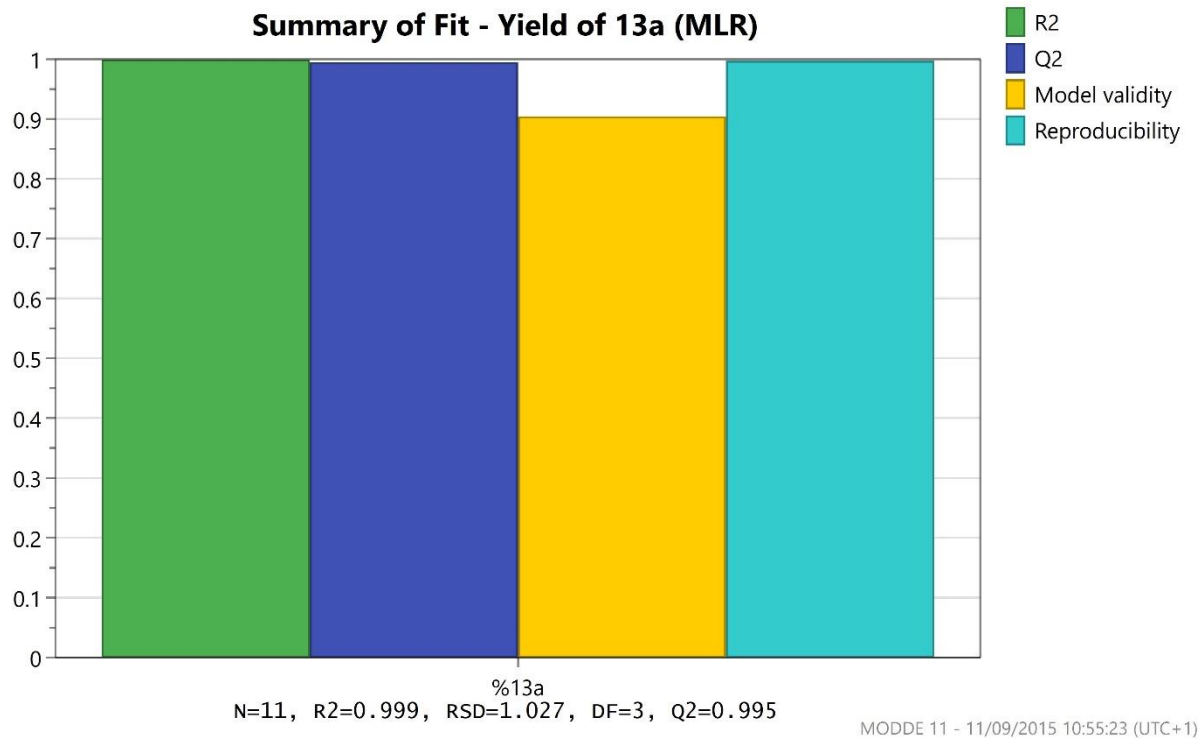
A mixture of aryl chloride **11** (1 eq) and 3-amino-5-methylpyrazole **12** (2 eq) in the solvent stated was heated in the microwave at the stated time and temperature. The reaction mixture was cooled to RT before concentrating *in vacuo*. The crude reaction residue was dissolved in CH_3OH until all the residue was in solution and 1,3,5-trimethoxybenzene (0.28M in CH_3OH, 500 µL) added. An aliquot was removed, concentrated *in vacuo* and then dissolved in CD_3OD for NMR analysis. Conditions and quantities for each reaction are illustrated in the table below.

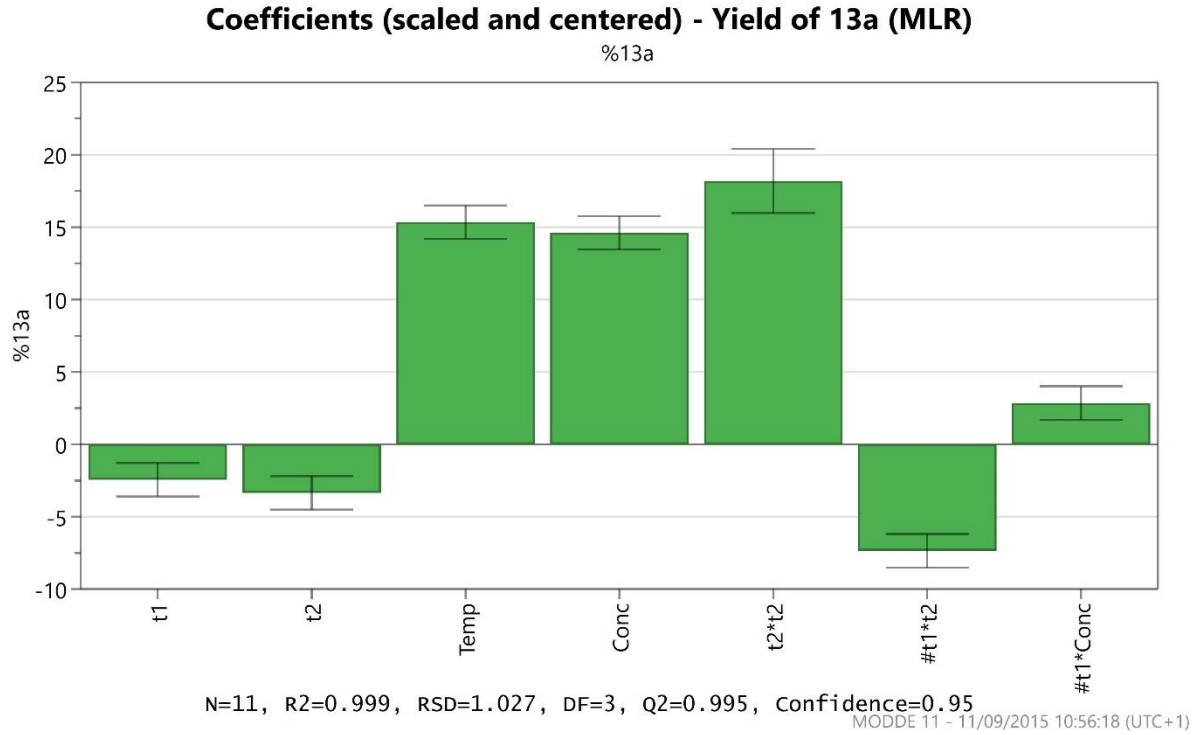
Run Order	Solvent	Temp (°C)	Conc (M)	Volume (mL)	11 (mmol)	11 (mg)	12 (mmol)	12 (mg)
1	EtCN	120	0.3	2	0.60	96	1.20	117
2	CPME	140	0.1	2	0.20	32	0.40	39
3	Pr_2O	140	0.5	2	1.00	160	2.00	194
4	*n*BuOH	140	0.1	2	0.20	32	0.40	39
5	*n*BuOH	100	0.5	2	1.00	160	2.00	194
6	Pr_2O	100	0.1	2	0.20	32	0.40	39
7	DMA	140	0.5	2	1.00	160	2.00	194
8	CPME	100	0.5	2	1.00	160	2.00	194
9	EtCN	120	0.3	2	0.60	96	1.20	117
10	EtCN	120	0.3	2	0.60	96	1.20	117
11	DMA	100	0.1	2	0.20	32	0.40	39

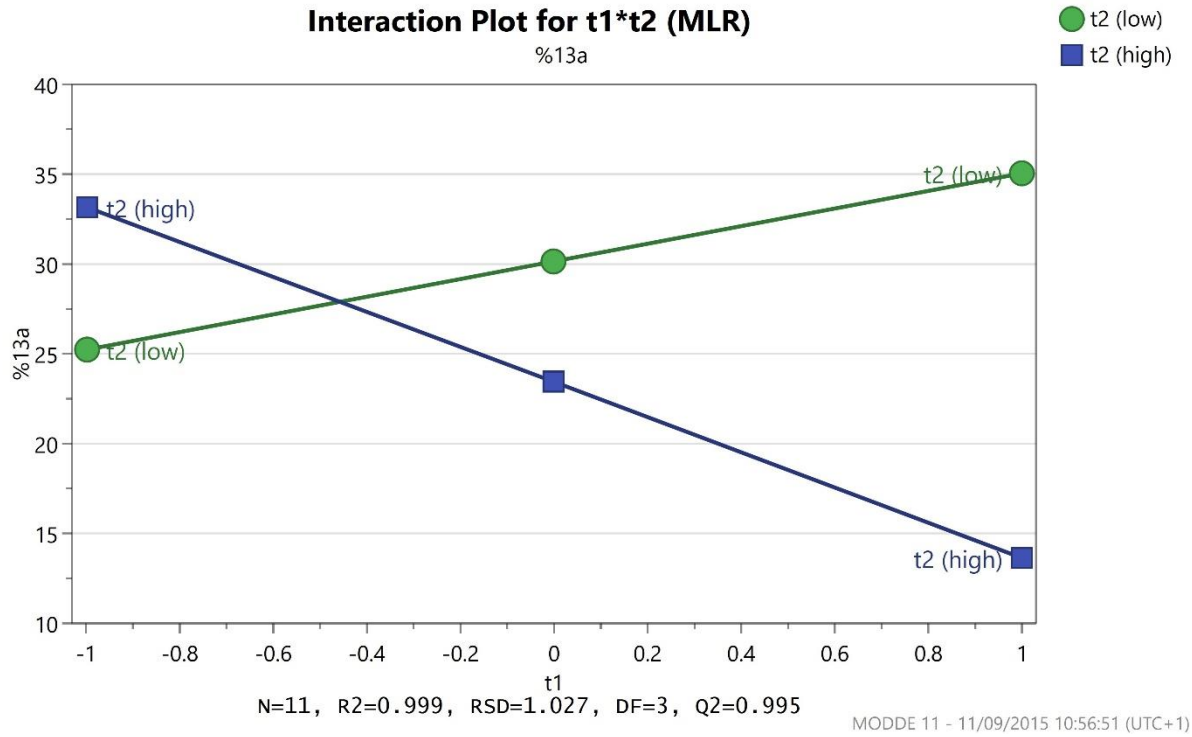
Results of the Second DoE Experiments

Run Order	t1	t2	Temp	Conc	%13a	%13b	%13c	%SM
1	0	0	120	0.3	7.2	3.2	1.1	72.6
2	1	1	140	0.1	11.3	2.2	1.2	72.9
3	1	-1	140	0.5	67.6	3.6	3.3	6.7
4	-1	-1	140	0.1	29	5.5	3.1	54.8
5	-1	-1	100	0.5	21.4	1.9	0.8	33.7
6	1	-1	100	0.1	2.4	0	0	99.3
7	-1	1	140	0.5	60.5	7.1	4	0*
8	1	1	100	0.5	15.9	1.4	0.7	66.5
9	0	0	120	0.3	9.4	4.3	1.5	90.9
10	0	0	120	0.3	9.1	4.1	1.5	88.5
11	-1	1	100	0.1	5.9	1.1	0.7	71.3

*23.4% yield of **13d** was also observed in this reaction.




Coefficients (scaled and centered) - Yield of 13a (MLR)
%13a
25
20
15
10
5
0
-5
-10
%13a
t1
t2
Temp
Conc
t2*t2
#t1*t2
#t1*Conc
N=11, R2=0.999, RSD=1.027, DF=3, Q2=0.995, Confidence=0.95
MODDE 11 - 11/09/2015 10:56:18 (UTC+1)


Interaction Plot for t1*t2 (MLR)
%13a
t2 (low)
t2 (high)
40
35
30
25
20
15
10
%13a
t2 (high)
t2 (low)
t2 (low)
t2 (high)
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
t1
N=11, R2=0.999, RSD=1.027, DF=3, Q2=0.995
MODDE 11 - 11/09/2015 10:56:51 (UTC+1)

4. Crystallographic Data for 13b and 13c

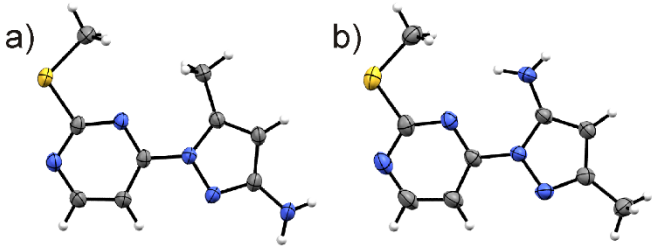


Figure 8. Molecular structures of compounds: a) **13b** and b) **13c**, as determined by single crystal X-ray diffraction.

Single Crystal X-ray Diffraction

Single X-ray diffraction data was collected using an *Agilent SuperNova (Dual Source)* single crystal X-ray diffractometer equipped with an *Atlas CCD Detector*. The data were collected 150 K (**13b**) and 200 K (**13c**) using CuK_α radiation (λ = 1.54184 Å). The data were collected and processed using the *CrysAlisPro* program.[1] Empirical absorption correction was performed using spherical harmonics implemented in the *SCALE3 ABSPACK* scaling algorithm. Structure solution and refinement were accomplished using *SHELXS-97* and *SHELXL-97*, respectively.[2] The structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms associated with carbon and nitrogen atoms were refined isotropically. Crystallographic and refinement parameters for crystal structures **13b** and **13c** are given in Table S1.

1. CrysAlisPro, Agilent Technologies, Version 1.171.36.28 (release 01-02-2013 CrysAlis171 .NET).
2. Sheldrick, G. M. *Acta Crystallogr. A.* **2008**, *64*, 112–122.

Table S1. Crystallographic and refinement parameters for compounds **13b** and **13c**.

compound	**13b**	**13c**
empirical formula	$C_9H_{11}N_5S$	$C_9H_{11}N_5S$
M_r / g mol^{-1}	299.32	299.32
T / K	150.00(10)	200.00(10)
crystal system	monoclinic	orthorhombic
space group	$P2_1/c$	$Pca2_1$
a / Å	7.54390(10)	21.0057(3)
b / Å	23.3450(4)	4.06460(10)
c / Å	5.85840(10)	12.0663(2)
α / °	90	90
β / °	96.946(2)	90
γ / °	90	90
V / Å^3	1024.16(3)	1030.22(3)
Z	4	4
ρ_{calc} / g cm^{-3}	1.435	1.427
μ / mm^{-1}	2.598	2.582
F(000)	464	464
crystal size / mm^3	0.21 × 0.14 × 0.05	0.35 × 0.17 × 0.06
X-ray radiation	CuK_α (λ = 1.5418 Å)	CuK_α (λ = 1.5418 Å)
index ranges	$-8 \le h \le 8$	$-26 \le h \le 26$
	$-27 \le k \le 27$	$-4 \le k \le 4$
	$-6 \le l \le 6$	$-14 \le l \le 14$
no. of reflections measured	14217	13406
no. independent reflections	1797	2040
R_{int} [$I \ge 2\sigma(I)$]	0.0353	0.0300
goodness-of-fit on F^2	1.046	1.063
final R_1 values [$I \ge 2\sigma(I)$]	0.0314	0.0261
final $wR(F^2)$ values [$I \ge 2\sigma(I)$]	0.0843	0.0674
final R_1 values [all data]	0.0339	0.0272
final $wR(F^2)$ values [all data]	0.0875	0.0684
largest diff. peak/hole / e Å^{-3}	0.204 / -0.252	0.141 / -0.188
CCDC deposition number	1423525	1423524

5. References

1. C. Körner, P. Starkov, T. D. Sheppard, *J. Am. Chem. Soc.* **2010**, *132*, 5968.
2. C. Brouwer, C. He, *Angew. Chem. Int. Ed.* **2006**, *45*, 1744.
3. A. R. Katritzky, G. Baykut, S. Rachwal, M. Szafran, K. C. Caster and J. Eyler, *J. Chem. Soc., Perkin Trans. 2*, 1989, **10**, 1499 – 1506
4. J Charrier, F. Mazzei, D. Kay and A. Miller, **2004**, *Processes for preparing substituted pyrimidines and pyrimidine derivatives as inhibitors of protein kinase*, WO2004000833