A combined experimental and natural bonding orbital charges study on the one-pot regioselective synthesis of 4-chloropyrazoles

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The mechanism of a DMF-catalysed electrophilic/nucleophilic chlorination of pyrazole is illustrated with the aid of calculations of the natural bonding orbital charges. Its high regioselectivity and good functionality tolerance of nine pyrazole substrates have been experimentally demonstrated.

Keywords: chlorinated pyrazoles, small molecular catalysis, electrophilic substitution, nucleophilic substitution, natural bonding orbital charges calculations

The discovery of the acaricide tebufenpyrad,[1] insecticide tolfenpyrad,[2] and herbicide pyraflufen-ethyl (Fig. 1),[3] 4-chloropyrazoles have attracted considerable attention due to their diverse bioactivities such as antimicrobial (**A**)[4] and herbicidal (**B**) activities.[5] Chen *et al.*[6] has synthesised a series of substituted 4-chloropyrazoles (**C**) for the control of *Rhizoctonia solani*.[6] These 4-chloropyrazoles (**2**) containing a useful functional handle (chloro atom) at the 4-position, have also been employed as participants in cross-coupling reaction.[7–9] However, existing methods for direct access to **2** are limited. Although it can be prepared by chlorination with the use of *N*-chlorinated succinimide or sulfuryl dichloride,[10–12] or *via* condensation between hydrazines and acrylates or 1,3-dicarbonyl precursors,[13–15] these methods suffer from poor regioselectivity, limited substrate scope, multi-step syntheses, or costly purification. Thus, the development of new approaches to **2** that avoid these limitations will be of great value. Our group has devoted considerable effort to address this issue, and has reported a novel DMF-catalysed 4-chlorination of 3-oxypyrazoles with good functionality tolerance.[16]

To further explore its scope, in this paper, nine pyrazole substrates **1a**–**h** with many functional groups have been synthesised, and their direct chlorination is investigated. In addition, the chlorination mechanism is illustrated with the aid of calculations of the natural bonding orbital (NBO) charges.

Results and discussion

The reaction of 1-phenyl-1*H*-pyrazol-3-ol (**1a**) with $SOCl_2$ was selected as a model, and the following results were obtained to illustrate its chlorination mechanism: (1) with a catalytic amount of DMF, a higher yield of **2a** (Scheme 1, 81%) was obtained than without DMF; (2) the $SOCl_2$–DMF (**SD**) complex was prepared to determine whether the **SD** complex was the chlorinating species (Scheme 2), and was allowed to react with **1a** in boiling $CHCl_3$. However, only a trace of product **2a** was detected by HPLC. Therefore, it seems most likely that **1a** reacts with $SOCl_2$ first, and then the reaction with catalyst DMF occurs; (3) the 4-chlorination likely proceeds *via* a nucleophilic attack by Cl^-; because $SOCl_2$ is normally a source of Cl^-, and the intermediacy of Cl^- is feasible; (4) the natural bonding orbital (NBO) charges of **1a** indicated that the C4 (–0.4) atom of the pyrazole ring had more negative charges than C5 (–0.02), and the initial electrophilic attack of $SOCl_2$ should occur at C(4) atom (Scheme 1); and (5) elemental sulfur was isolated during the purification of **2a**.

We propose a catalytic mechanism for the formation of **2a** (Scheme 3). As can be seen from the NBO charges of **1a**, the initial electrophilic attack of $SOCl_2$ occurs at the more electron-rich C(4) atom (–0.4) [C(5) (–0.02)], generating an unstable intermediate **I** and releasing one molecule of HCl. Subsequently, the system goes through a transition state **II**, in which the complexation of **I** with DMF donates a delocalised Cl^- to nucleophilic substitute the SO-DMF group, then yield **2a** and regenerate DMF. The catalyst DMF acts as an electron-withdrawing group to accelerate the reaction rate and as a leaving group upon protonation. Although SO has not been detected, elemental sulfur was isolated, indicating the possible involvement of SO in the reaction.

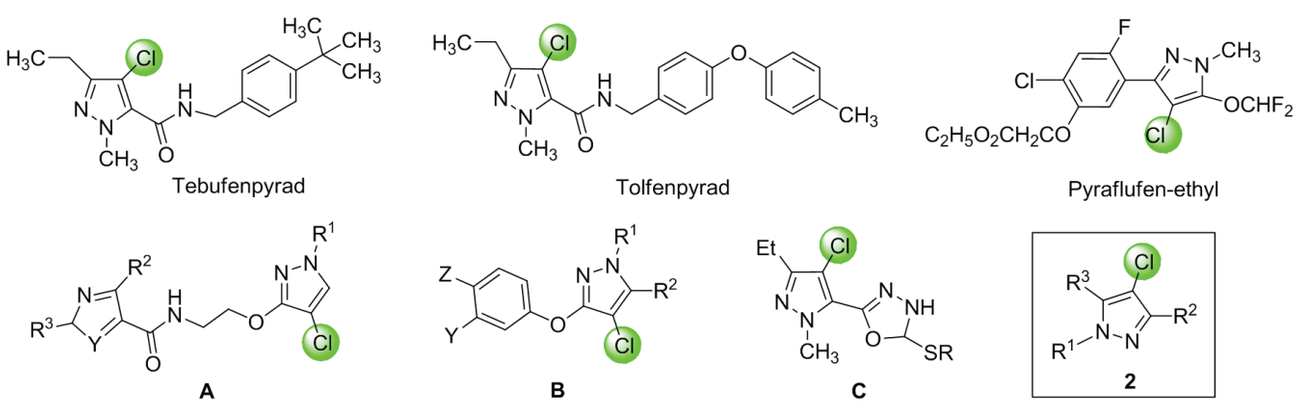

Fig. 1 Design strategy for the target product **1**.

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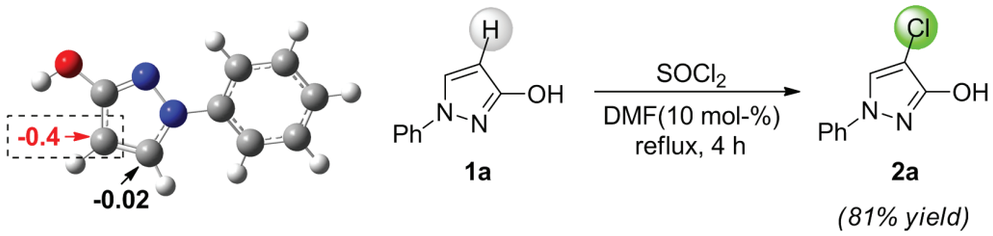
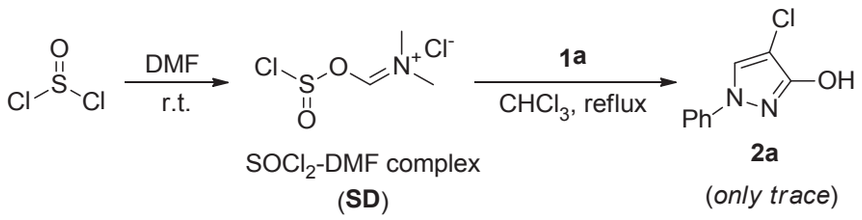
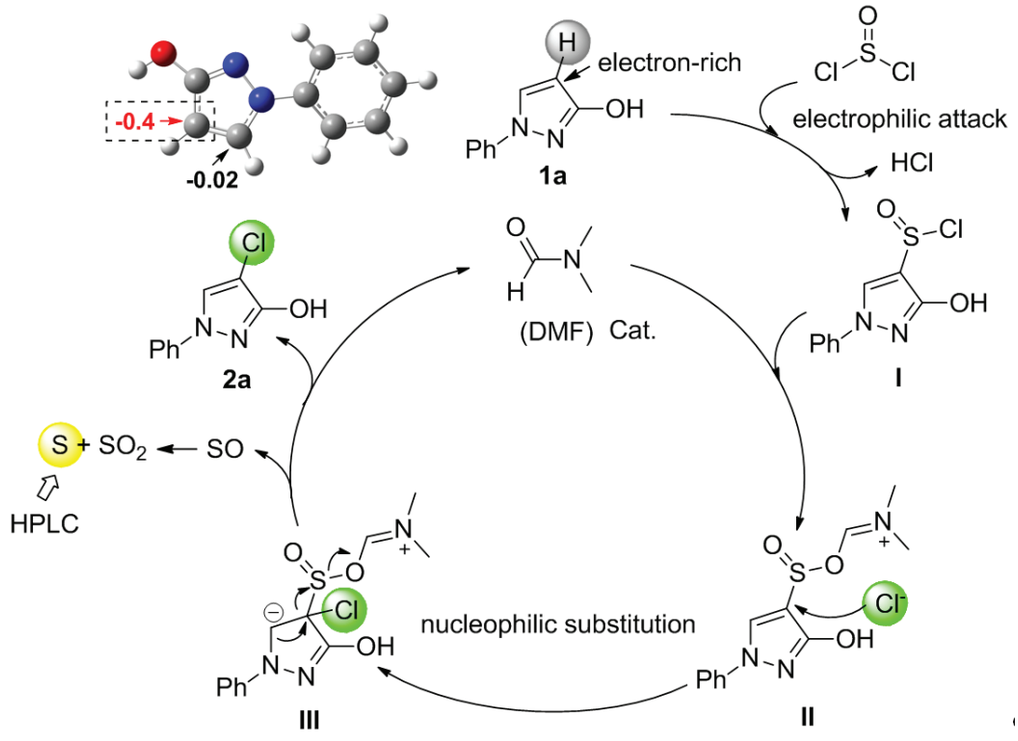


Scheme 1 DMF-Catalysed 4-chlorination of 1-phenyl-1*H*-pyrazol-3-ol (**1a**).



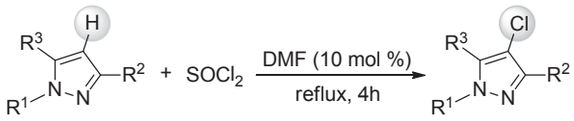
Scheme 2 Reaction of **1a** with $SOCl_2$–DMF complex (**SD**).



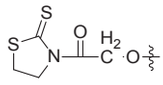
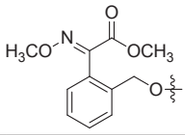
Scheme 3 Proposed reaction pathway for the formation of **2a** from **1a**.

To further investigate its scope and regioselectivity, pyrazole substrates **1b**–**i** with alkyl or aryl groups at the 1- or 5-position, with alkyl, alkoxy, hydroxyl, or *O*-amide groups at the 3-position, were synthesised for chlorination in boiling $SOCl_2$ by using DMF (10 mol%) as catalyst (Table 1). The 1-aryl-substituted 3-hydroxylpyrazoles **1b** with an electron-donating group, and **1c** with an electron-withdrawing group on the 1-phenyl ring, giving 80% and 78% yield of **2b** and **2c**, respectively, with high regioselectivity for monochlorination at the 4-position. The chlorination of ethoxypyrazole **1d** or methylpyrazole **1e** without substitution on the N-atom also proceeded well, and 76% yield of **2d** and 68% yield of **2e** were isolated. However, substrate **1f** containing an *O*-amide group, gave a slightly lower yield (60%) of **2f**, possibly due to the partial hydrolysis of the amide moiety under acidic conditions. In addition, 3,5-dimethylpyrazoles **1g** with phenyl group on the N-atom, underwent better chlorination than **1h** with methyl group (giving 75% or 70% yield of the 4-chlorinated products **2g** and **2h**, respectively). Compound **1i** containing many useful functional groups, such as alkoxy, ester, imino, and aryl groups, with both electron-donating and -withdrawing groups, was also compatible with this direct 4-chlorination, and the procedure allowed the regioselective formation of **2i** in 82% yield. Significantly, this direct chlorination can avoid tedious steps of protection and deprotection of functional groups. Compared to the other methine C-atom, the C(4) atom of the pyrazole ring shows more electron-rich to make the electrophilic attack of $SOCl_2$ and the nucleophilic substitution

Table 1 DMF-catalysed 4-chlorination of substrates **1a–i** with $SOCl_2$



1a-1i **2a-2i**

Substrate	R^1	R^2	R^3	Yield/%
1a	Ph	OH	H	81 (**2a**)
1b	*p*-$CF_3OC_6H_4$	OH	H	80 (**2b**)
1c	*m*-$CF_3C_6H_4$	OH	H	78 (**2c**)
1d	H	OEt	Ph	76 (**2d**)
1e	H	Me	Me	68 (**2e**)
1f	Ph		*p*-MeC_6H_4	60 (**2f**)
1g	Ph	Me	Me	75 (**2g**)
1h	Me	Me	Me	70 (**2h**)
1i	*p*-ClC_6H_4		H	82 (**2i**)

of Cl^- only take place at. With the help of the NBO charges calculations, the probability and position of this chlorination on the pyrazole ring can be speculated. The regioselectivity of this chlorination and structural elucidation of the products were unequivocally determined by ^1H NMR spectra and single-crystal X-ray diffraction analysis of **2f** (Fig. 2).

Experimental

All reagents were of analytical grades. High-performance liquid chromatography was recorded on a P680 chromatograph (column: Kromasil 100-5C18; mobile phase: methanol/ultra-pure water, 3 : 1; flow: 0.6 mL min^{-1}). Column chromatography was carried on flash silica gel (300–400 mesh) by using mixtures of ethyl acetate and petroleum ether as eluent. Melting points were measured on an X-4 microscope electrothermal apparatus (Taike, China) and were uncorrected. ^1H NMR spectra were recorded in [D_6]DMSO or $CDCl_3$ with Bruker AV-300 (300 MHz), AV-400 (400 MHz), or AV-500 (500 MHz) spectrometers, with tetramethylsilane as an internal standard. Elemental analyses were performed on a Flash EA-1112 elemental analyser.

Synthesis of pyrazole substrates **1a–h***; general procedure*

Compounds **1a–c** were prepared from ethyl acrylate *via* two steps including addition–cyclisation and oxidation.[16,17] Compounds **1d** and **1f** were prepared according to the literature.[16] Compounds **1e**, **1g** and **1h** were synthesised by the reaction of acetyl acetone and hydrazine derivatives under alkaline conditions.[18] Spectral data of **1a–h** match those previously reported.[16–18]

Synthesis of pyrazole substrate **1i***; general procedure*

K_2CO_3 (0.35 g, 2.5 mmol) was added to a solution of 1-(4-chlorophenyl)-1*H*-pyrazol-3-ol (0.19 g, 1.0 mmol) in acetone (30 mL). Then methyl (*E*)-2-[2-(bromomethyl)phenyl]-2-(methoxyimino)acetate (0.3 g, 1.05 mmol) was added slowly. The mixture was refluxed for 4 h, filtered, and solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: AcOEt/petroleum ether, 1 : 12 v/v) to afford pyrazole substrate **1i**.

*Methyl (E)-2-[2-({[1-(4-chlorophenyl)-1*H*-pyrazol-3-yl]oxy}methyl) phenyl]-2-(methoxyimino)acetate* (**1i**): White solid; m.p. 131–132 °C; yield 0.33 g (82%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=2.4 Hz, 1H, CH), 7.62–7.19 (m, 8H, ArH), 5.85 (d, J=2.4 Hz, 1H, CH), 5.18 (s, 2H, CH_2), 4.08 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); Anal. calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51; found: C, 59.85; H, 4.59; N, 10.58%.

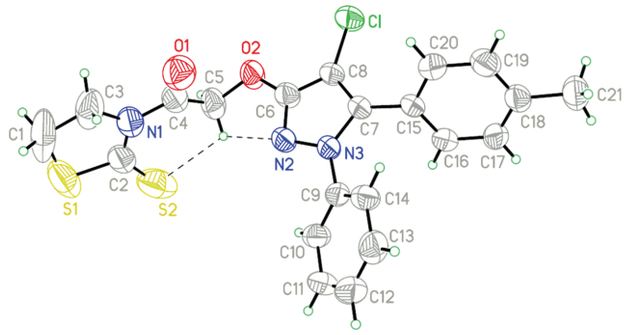


Fig. 2 ORTEP Plot of the molecular structure of **2f** showing atom-numbering scheme; 50% probability thermal ellipsoids.

Synthesis of 4-chlorinated pyrazoles **2a–I***; general procedure*

$SOCl_2$ (5 mL) was added to a round-bottom flask, and then **1a–i** (1.0 mmol) and a catalytic amount of DMF (0.1 mmol) were added. The mixture was heated to reflux for 4 h (reaction monitored by HPLC), then excess $SOCl_2$ was evaporated under reduced pressure. The residue was dispersed in H_2O (200 mL) and extracted with AcOEt. The organic phase was separated, dried, and concentrated. It was then purified by flash column chromatography (eluent: ethyl acetate/petroleum ether, 1 : 10 v/v) to afford **2a–i**.

*4-Chloro-1-phenyl-1*H*-pyrazol-3-ol* (**2a**): White crystals; m.p. 180–181 °C (lit.[12] 179–181 °C); yield 0.16 g (81%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H, OH), 8.54 (s, 1H, CH), 7.69–7.21 (m, 5H, ArH); Anal. calcd for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.39; found: C, 55.75; H, 3.58; N, 14.32%. The spectral data match those previously reported.[12]

*4-Chloro-1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazol-3-ol* (**2b**): White crystals; m.p. 137–138 °C; yield 0.22 g (80%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H, CH), 7.40 (d, J=8.8 Hz, 2H, ArH), 7.25 (d, J=8.8 Hz, 2H, ArH); Anal. calcd for $C_{10}H_6ClF_3N_2O_2$: C, 43.11; H, 2.17; N, 10.05; found: C, 43.31; H, 2.14; N, 10.13%.

*4-Chloro-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazol-3-ol* (**2c**): White crystals; m.p. 112–113 °C; yield 0.21 g (78%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H, CH), 7.64 (t, J=7.6 Hz, 2H, ArH), 7.55 (t, J=7.6 Hz, 1H, ArH), 7.47 (d, J=7.6 Hz, 1H, ArH); Anal. calcd for $C_{10}H_6ClF_3N_2O$: C, 45.73; H, 2.30; N, 10.67; found: C, 45.55; H, 2.34; N, 10.75%.

*4-Chloro-3-ethoxy-5-phenyl-1*H*-pyrazole* (**2d**): Yellow oil; yield 0.17 g (76%); ^1H NMR (DMSO-d_6, 500 MHz) δ 12.66 (s, 1H, NH), 7.70–7.43 (m, 5H, PhH), 4.24 (q, J=7.0 Hz, 2H, CH_2), 1.34 (t, J=7.0 Hz, 3H, CH_3); Anal. calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58; found: C, 59.55; H, 4.93; N, 12.67%. The spectral data match those previously reported.[16]

*4-Chloro-3,5-dimethyl-1*H*-pyrazole* (**2e**): White crystals; m.p. 116–117 °C (lit.[10] 117–118 °C); yield 0.09 g (68%); ^1H NMR ($CDCl_3$, 300 MHz) δ 11.83 (s, 1H, NH), 2.26 (s, 6H, CH_3); Anal. calcd for $C_5H_7ClN_2$: C, 45.99; H, 5.40; N, 21.45; found: C, 45.78; H, 5.45; N, 21.53%. The spectral data match those previously reported.[10]

*2-{[4-Chloro-1-phenyl-5-(*p*-tolyl)-1*H*-pyrazol-3-yl]oxy}-1-(2-thioxothiazolidin-3-yl)ethanone* (**2f**): Yellow crystals; m.p. 195–196 °C; yield 0.27 g (60%); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27–7.14 (m, 9H, ArH), 5.78 (s, 2H, CH_2), 4.61 (t, J=7.6 Hz, 2H, CH_2), 3.38 (t, J=7.6 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3); Anal. calcd for $C_{21}H_{18}ClN_3O_2S_2$: C, 56.81; H, 4.09; N, 9.46; found: C, 56.58; H, 4.03; N, 9.52%.

*4-Chloro-3,5-dimethyl-1-phenyl-1*H*-pyrazole* (**2g**): Yellow oil; yield 0.16 g (75%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48–7.32 (m, 5H, PhH), 2.35 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); Anal. calcd for $C_{11}H_{11}ClN_2$: C, 63.93; H, 5.36; N, 13.55; found: C, 63.72; H, 5.31; N, 13.63%. The spectral data match those previously reported.[10]

*4-Chloro-1,3,5-trimethyl-1*H-*pyrazole* (**2h**): Yellow oil; yield 0.1 g (70%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.67 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); Anal. calcd for $C_6H_9ClN_2$: C, 49.84; H, 6.27; N, 19.37; found: C, 49.65; H, 6.21; N, 19.46%. The spectral data match those previously reported.[10]

Methyl (E)*-2-[2-({[4-chloro-1-(4-chlorophenyl)-1*H*-pyrazol-3-yl] oxy}methyl)phenyl]-2-(methoxyimino)acetate* (**2i**): White solid; m.p. 147–148 °C (lit.[19] 147–148 °C); yield 0.36 g (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H, CH), 7.61–7.20 (*m*, 8H, ArH), 5.23 (*s*, 2H, CH_2), 4.03 (*s*, 3H, MeO), 3.84 (*s*, 3H, MeO); Anal. calcd for $C_{20}H_{17}Cl_2N_3O_4$: C, 55.31; H, 3.95; N, 9.68; found: C, 55.52; H, 3.91; N, 9.62%. The spectral data match those previously reported.[19]

X-ray crystallography

Crystal data were collected on a Nonius CAD-4 diffractometer by using MoK_α (0.71073 Å) radiation. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares on F^2 for all data using SHELXL-97.[20] All non-H-atoms were refined anisotropically, and the H-atoms were added at calculated positions. The isotropic temperature factors were fixed at 1.2 times (1.5 times for Me group) the equivalent isotropic displacement parameters of the C-atom to which the H-atom is attached.

CCDC-955904 contains the supplementary crystallographic data for **2f**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 3360-33; e-mail: deposit@ccdc.cam.ac.uk).

NBO charges calculations

The NBO charges calculations were carried out in the ground state (*in vacuo*) with Gaussian 09 software using the B3LYP/6-31G** method.[21,22]

Electronic Supplementary Information

The X-ray crystallographic analysis of **2f** and the NBO charges calculations of **1a–I** are available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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