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# A Michael Equilibration Model To Control Site Selectivity in the Condensation toward Aminopyrazoles

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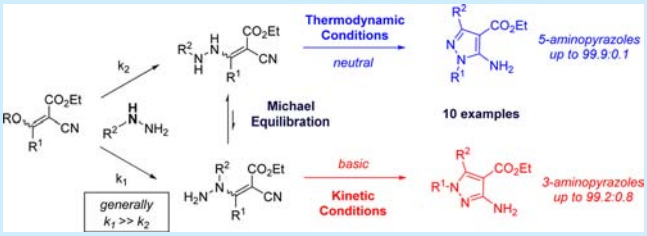
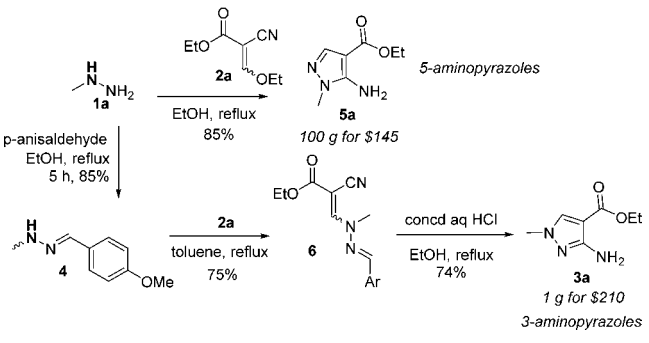
Supporting Information

**ABSTRACT:** A Michael equilibration model is presented to provide for site-selective pyrazole condensations between alkoxyacrylonitriles and hydrazines. Both pyrazole isomers were accessed with high selectivity by employment of kinetically or thermodynamically controlled conditions. Substrate scope and identification of Michael intermediates, as well as competitive pathways, support the presented mechanistic proposal. Sandmeyer derivatization provided site-selective access to fully substituted pyrazoles.




The pyrazole heterocycle has been a ubiquitous motif due to its incorporation into pharmaceuticals, agrochemicals, and materials as well as its natural occurrence.[1] Since the Knorr pyrazole synthesis[2] and related hydrazine condensation with alkoxymethylene malonates by Claisen and Haase,[3] numerous approaches toward the pyrazole core have been developed.[1,4] The addition and cyclization between hydrazines and alkoxyacrylonitriles, developed by Robins and Schmidt, has been a classical reaction toward aminopyrazoles.[5] In general, the 5-aminopyrazole isomer was favored through direct condensation.[5] Reversal of this presumed innate reactivity to access the opposite 3-aminopyrazole isomer required indirect approaches such as employing Schmidt and co-workers' multistep approach, developed in the late 1950s, to direct the initial Michael addition with a suitably protected hydrazine (Scheme 1).[6] Accordingly, specific isomers of aminopyrazoles, resulting from the direct condensation, are readily available while the opposite isomers have limited availability and can only be procured at high cost.[7] Rationalization for the site selectivity led to numerous, and at times conflicting, models that differ by the hydrazine and electrophile examined.[5,8] The common attribute was based on an initial nucleophilic attack to either the nitrile or activated olefin by the more nucleophilic substituted nitrogen of alkyl hydrazines or the unsubstituted nitrogen of aryl hydrazines.[2−6,8,9] Although the models provide reasonable rationales, they do not lead to general predictions or provide an avenue toward the uncommon isomer. Only sparse accounts for influence of reaction conditions or unusual site selectivity exist.[9b,d,10] However, the general consensus relates selectivity to the structure and electronic properties of the reactants. In contrast to these precedents, we report a Michael equilibration model to rationalize site selectivity in pyrazole condensations and to provide for high selectivity toward both the 3- and 5-aminopyrazoles.

**Scheme 1. General Approaches toward 3- and 5-Aminopyrazoles**[5c,6d,7]




The model system examined for the aminopyrazole condensation focused on the reaction between methyl hydrazine **1a** and ethyl 2-cyano-3-ethoxyacrylate **2a** with established protocols. Subjecting a solution of the electrophile to methyl hydrazine followed by the typical aging at elevated temperatures afforded an isomeric mixture with selectivity favoring the expected 5-aminopyrazole **5a** (Table 1). The selectivity toward the 5-aminopyrazole was modestly improved by utilizing a slight excess of the electrophile or by employing an ethereal solvent. A common mechanistic rationalization for the condensation relates to a rapid Michael addition followed by a slow intramolecular

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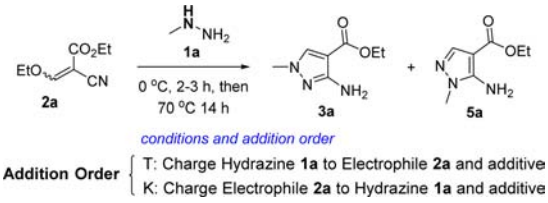
**Table 1. Identification of Site-Selective Pyrazole Condensation Conditions**[a]

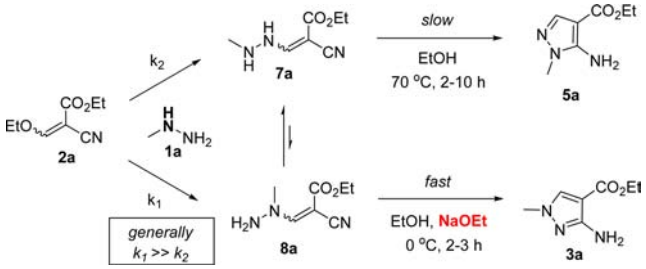



| entry | addition (time)[b] | stoich[c] (2a:1a) | conditions | ratio (3a:5a)[d] |
|---|---|---|---|---|
| 1 | T (5 min) | 1:1 | EtOH | 20:80 |
| 2 | T (60 min) | 1:1 | EtOH | 21:79[e] |
| 3 | T (60 min) | 1.05:1 | EtOH | 14:86 |
| 4 | T (60 min) | 1:1 | CPME | 15:85[f] |
| 5 | T (5 min) | 1:1 | AcOH, EtOH | 37:63 |
| 6 | T (5 min) | 1:1 | NaOEt, EtOH | 81:19 |
| 7 | K (60 min) | 1:1 | CPME | 53:47 |
| 8 | K (15 min) | 1:1 | NaOEt, EtOH | 94:6 |
| 9 | K (60 min) | 1:1 | NaOEt, EtOH | 99.2:0.8[g] |

[a]2 equiv of base or acid additive relative to electrophile **2a** was used. The base additive was neutralized with HCl before heating to 70 °C. [b]Addition order and duration. [c]Molar stoichiometry between **2a** to **1a**. [d]Site selectivity determined by HPLC. [e]56% crystallization yield to 1:99 ratio. [f]63% crystallization yield to 1:99 ratio. [g]83% crystallization yield. CPME = cyclopentyl methyl ether.

cyclization between the hydrazine and appended nitrile (Scheme 2).[2−5,11] However, the 5-aminopyrazole isomer would be derived

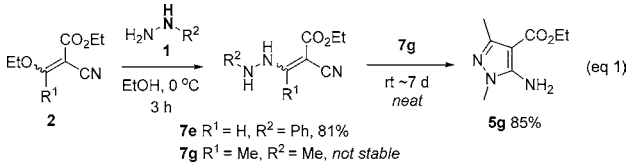
**Scheme 2. Mechanistic Rationale for Reversal in Site Selectivity**




from cyclization of adduct **7a** resulting from a Michael addition involving the less nucleophilic nitrogen of the methyl hydrazine.[8,9] A similar selectivity situation has been observed for the corresponding condensation with alkoxymethylenemalonates;[12] however, a couple of accounts have reversed this selectivity by using basic conditions.[9b,d,10b,13] Application of the sodium ethoxide conditions to the parent alkoxy-2-cyanoacrylate **2a** (entry 6) provided reasonable selectivity toward the 3-aminopyrazole, which is consistent with cyclization of adduct **8a** derived from the Michael addition with the more nucleophilic hydrazine nitrogen. The selectivity toward the 3-aminopyrazole was further improved to greater than 99:1 by reversing the addition order and employing a metered addition of the electrophile to the basic hydrazine solution (entry 9). Therefore, complementary conditions were established to access both isomers of the aminopyrazoles. The cyclization was also dramatically accelerated under basic conditions to be complete within 3 h at 0 °C in contrast to over 5 h at elevated temperatures under neutral conditions. This difference in cyclization rates provided for a reasonable rationalization to favor the 3-aminopyrazole by allowing the cyclization of the kinetic Michael adduct **8a** to effectively compete with the Michael equilibration. Conversely, the 5-aminopyrazole was favored under the neutral conditions due to cyclization of the Michael adduct **7a** that was generated from, and favored in, a Michael equilibration with the initially generated kinetic adduct **8a**.

The selectivity for the Michael addition between the nitrogen atoms of a monosubstituted hydrazine would be reasonably influenced by the steric and electronic properties of the substituent. Increasing the steric size of the hydrazine substituent from a methyl **1a** to a 2-phenylethyl **1d** and cyclohexyl **1b** group decreased the selectivity toward the 3-aminopyrazole from 99.2:0.8 to 97:3 and 72:28, respectively (Table 2). The most sterically demanding *tert*-butyl substituent **1c** reversed the selectivity to 5:95. Accordingly, the hydrazine substituent steric influence on the site selectivity was consistent with a competitive Michael alkylation between the hydrazine nitrogen atoms. The corresponding neutral, i.e., thermodynamic, conditions favored the 5-aminopyrazoles **5a−d** with increased selectivity in opposite order to the basic conditions consistent with the dynamic Michael intermediates. Aryl hydrazines are known to strongly favor 5-aminopyrazoles,[4−6,8] which was observed under the neutral conditions. However, employing the basic conditions with phenyl hydrazine **1e** provided an equal mixture of the pyrazoles **3e** and **5e**, which could be improved to favor the 3-aminopyrazole **3f** (78:22) by utilizing the more electronically donating *p*-methoxyphenyl hydrazine **1f**. The methodology to favor both the 3- and 5-aminopyrazoles under complementary conditions also tolerated the ethoxy 3-methyl-2-cyanoacrylate **2b** and malononitrile counterparts **2d** and **2e** for the Michael acceptor (entries 7, 8, 10, and 11).

The proposed thermodynamic Michael adducts have been reported and were typically derived from hydrazine[5b] or an aryl hydrazine[11,14] nucleophile. Accordingly, the thermodynamic Michael adduct **7e** derived from the reaction between phenyl hydrazine and the electrophile **2a** was isolated before cyclization by concentration and recrystallization of the reaction before heating to 70 °C (eq 1). The corresponding Michael adduct **7g**




derived from methyl hydrazine and electrophile **2b** was also isolated by a similar approach. However, the adduct was less stable and was only able to be characterized from the crude reaction concentrate wherein the neat oil cyclized upon storage at ambient temperature. In both systems, the kinetic Michael counterparts were not observed, and the subsequent pyrazole condensation (Table 2, entries 5 and 7) furnished the 5-aminopyrazoles **5e** and **5g** in high selectivities. Therefore, characterization of these Michael adducts further supported a thermodynamic Michael equilibrium toward the intermediate wherein the subsequent cyclization favored the 5-aminopyrazole.

The main rationale for the Michael equilibration model to generate 3-aminopyrazoles was establishing conditions for the cyclization of the kinetic Michael adducts to effectively compete with the equilibration. This acceleration in certain systems led to a cyclization toward the ester functional group competitively over the nitrile (eqs 2 and 3). Utilization of 2-hydroxyethyl hydrazine **1g** or the isopropyl-substituted electrophile **2c** under the kinetic conditions furnished the amide adducts **9** and **10**,


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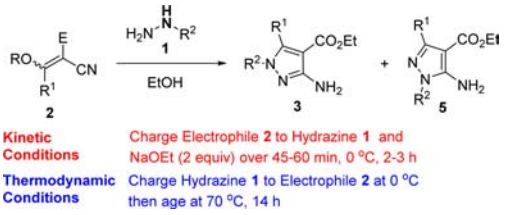
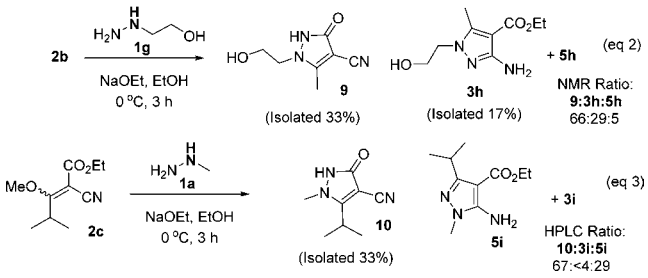
**Table 2. Scope for the Site-Selective Pyrazole Synthesis**[a]




| Entry | Reactants 2, 1 | Reaction Selectivity (3:5)[b] Kinetic Cond. 3 Yield[c] | Thermo. Cond. 5 Yield[c] |
|---|---|---|---|
| 1 | 2a + 1a | 3a, 83% (99.2:0.8) | 5a, 63%[d] (15:85) |
| 2 | 2a + 1b HCl | 3b, 58% (72:28) | 5b, 68% (0.7:99.3) |
| 3 | 2a + 1c HCl | 3c, 4% (5:95) | 5c, 94% (<0.1:99.9) |
| 4 | 2a + 1d $H_2SO_4$ | 3d, 81% (97:3) | 5d, 67% (4:96) |
| 5 | 2a + 1e | 3e, 41% (50:50) | 5e, 87% (<0.1:99.9) |
| 6 | 2a + 1f HCl | 3f, 54% (78:22) | 5f, 71% (0.1:99.9) |
| 7 | 2b + 1a | 3g, 74% (97:3) | 5g, 82% (0.2:99.8) |
| 8 | 2b + 1g | 3h, 17%[e] (86:14) | 5h, 97% (1.3:98.7) |
| 9 | 2c + 1a | 3i, ND[f] | 5i, 83% (<4:96) |
| 10 | 2d + 1a | 3j, 65% (96:4) | 5j, 49% (15:85) |
| 11 | 2e + 1a | 3k, 75% (96:4) | 5k, 73% (3:97) |

[a]Reactions conducted under either kinetic or thermodynamic conditions as indicated. An additional 1 or 2 equiv of sodium ethoxide employed if necessary to compensate for the equivalency of acid introduced by the hydrazine. [b]Reaction selectivity between the 3-amino- (**3**) and 5-aminopyrazoles (**5**) determined by HPLC. [c]Unoptimized isolated yield after crystallization or purification to >99:1 isomeric ratio. [d]CPME employed as the reaction solvent. [e]Major adduct was compound **9**. [f]Not determined; see eq 3.

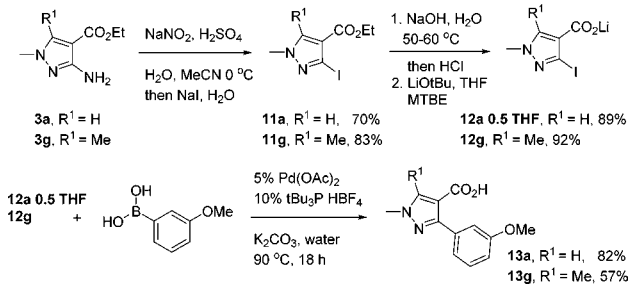
respectively, as the predominant products. The corresponding reactions under thermodynamic conditions strongly favored the 5-aminopyrazoles **5h** and **5i** (Table 2, entries 8 and 9). The two adducts **9** and **10** reflect substrates which biased the cyclization




toward the ester. The hydroxy substituent within the hydrazine **1g** may have participated in the cyclization such as by generating an 1,4-oxazepine intermediate[15] and directed the cyclization toward the ester. Alternatively, the isopropyl substituent within electrophile **2c** reasonably biased the *E*/*Z* geometry of the Michael intermediate to position the hydrazine and ester functional groups in a *syn* relationship to minimize steric strain involving the larger isopropyl group by positioning the substituent *syn* to the smaller nitrile. In both cases, the ester cyclization observed under the basic conditions occurred from the kinetic Michael adducts and proceeded with a different chemoselectivity than observed under the thermodynamic conditions.

Economical access to the uncommon 3-aminopyrazoles provided an opportunity for greater diversity of the respective derivatives and applications. The Sandmeyer reaction for 5-aminopyrazoles has significant precedence,[16] while the corresponding derivatization of 3-aminopyrazoles was less common.[17] Conversion of the 3-aminopyrazoles **3a** and **3g** to the iodopyrazoles **11a** and **11g** proceeded in good yield under standard conditions wherein the iodide Sandmeyer variant was employed to circumvent the use of copper salts (Scheme 3).

**Scheme 3. Application**




Saponification followed by conversion to the lithium carboxylates allowed for isolation of crystalline materials as the tetrahydrofuran hemisolvate for the intermediate **12a** and unsolvated form for adduct **12g**. Utilization of these lithium salts allowed a Suzuki coupling to be conducted in water[18] and provided access to derivatize the 3-position of the 3-aminopyrazoles as well as the site-selective preparation of a fully substituted pyrazole **13g**.

In conclusion, a detailed study on the site selectivity in the condensation of hydrazines and alkoxy 2-cyanoacrylates is presented. The results support a dynamic Michael intermediate equilibrium which when appropriately addressed can provide access to both the 3- and 5-aminopyrazoles in high selectivity. Application of this model to the classical Schmidt multistep approach toward 3-aminopyrazoles indicated that the resulting selectivity with use of the protected hydrazine was due to elimination of the Michael equilibration rather than regiose-



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lective control of the presumed initial Michael addition. Most importantly, the site-selective preparation of 3-aminopyrazoles[19] from cost-effective materials will enhance their availability and utility for the chemical community.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, NMR spectra, and elucidation of site isomers. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01248.

## ■ AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.

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