An Expedient Synthesis of Regioisomeric Pyrazole-Fused Cycloalkanones

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Abstract: Described herein is a novel one-pot procedure for the synthesis of pyrazoles through the in situ generation of a monohydrazone of cyclic 1,3-diones and subsequent cyclization with *N*,*N*-dimethylformamide dimethyl acetal. This route provides pyrazoles that have limited accessibility by other methods.

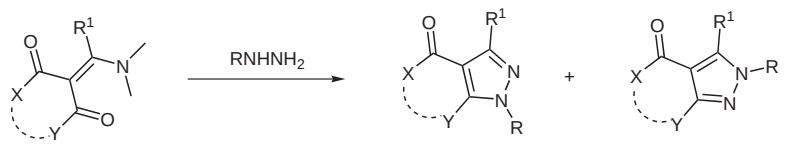
Key words: pyrazole, hydrazine, hydrazone, fused-ring system, dione

Though rarely found in nature, pyrazoles receive considerable attention from the synthetic and medicinal chemistry communities. The employment of enaminediones **1** for generating polysubstituted pyrazoles **2** and **3** is well established (Scheme 1).[1–5] Use of this synthon has flourished since its introduction.[1a] The ability of enaminediones and 1,2- and 1,3-dinucleophiles to form diverse heterocycles continues to attract attention and innovation.[2a] The preparation of pharmaceutically relevant pyrazoles from enaminediones has been the focus of recent medicinal chemistry efforts.[4]

Enaminediones **1** are typically more reactive than enaminones. This heightened reactivity has been attributed to resonance stabilization from delocalization of the negative charge across two carbonyls, as depicted by the mesomeric structure **4** (Scheme 2).[1a,3] This configuration is thought to favor attack of the primary amino group of a substituted hydrazine at the exocyclic carbon, leading to pyrazole **2** (Scheme 1).[1a,2a] This reaction proceeds via initial addition–elimination amine-exchange of the dimethylamino group by the hydrazine to afford the hydrazinomethylene adduct **5**, which then undergoes concomitant cyclodehydration to afford pyrazole **2** (Scheme 2). Alternately, it has been suggested that regioisomer **3** originates from attack of the primary amino group of the hydrazine first with a carbonyl, forming an intermediate hydrazone **6** (Scheme 2), followed by cyclization to **3**.[1a] However, it seems equally plausible that pyrazole **3** could arise from attack of the secondary amino group at the exocyclic carbon, followed by cyclization to **3**.

Based on literature reports, treatment of an acyclic, symmetrical enaminedione **1** with methylhydrazine affords a mixture of regioisomeric pyrazoles **2**/**3** (Scheme 1, X, Y = alkyl, aryl, R^1 = H).[1a,2b] However, the analogous reaction with phenylhydrazine is generally regiospecific, forming only pyrazole **2**.[1a,5] Five-membered cyclic enaminediones and hydrazines are often quite reluctant to provide pyrazoles.[1a,2a] In six-membered cyclic systems (Scheme 1, X–Y = alkyl, substituted alkyl, R^1 = H) regioisomer **2** again predominates, and **3** is rarely observed regardless of the substitution of the hydrazine (**2**/**3** = 19:1 to >99:1).[1a,2a] Only one example has been previously reported in the literature for seven-membered cyclic systems.[2a]

Heterocycle-fused cycloalkanones were required as part of a structure–activity relationship survey in a medicinal chemistry program.[6] Cycloheptapyrazolones, such as **2a**–**d** and **3a**–**d** (vide infra), were identified as desirable intermediates. The use of enaminediones was selected as a versatile means of accessing the preferred pyrazoles. The prerequisite enaminedione **1a** was prepared from 1,3-cycloheptane dione and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA).[1a] Treatment of **1a** at 0 °C with methylhydrazine in methanol afforded pyrazoles **2a**/**3a** in good yield as a 5:1 mixture of regioisomers (Table 1, entry 1).[7–11] In an attempt to improve the regioselectivity the reaction was repeated at –78 °C, which unexpectedly reversed the regioselectivity, now favoring formation of pyrazole **3a** (**2a**/**3a** = 1:3). The reaction of **1a** and methylhydrazine in refluxing methanol provided pyrazoles **2a**/**3a** with improved regioselectivity (**2a**/**3a** = 10:1), though in reduced yield. Other substituted hydrazines varied from this result (Table 1).[10]



Scheme 1

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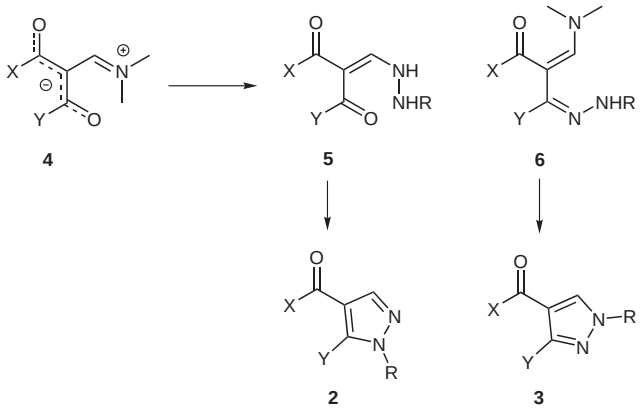
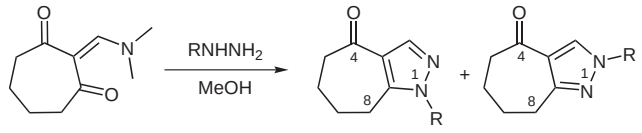


Scheme 2

Table 1 Cycloheptapyrazolones[7,10]



Entry	R	Ratio of **2**/**3** (yield, %)		
		–78 °C	0 °C	65 °C
1	Me (**a**)	1:3 (91)	5:1 (86)	10:1 (56)
2	Et (**b**)	11:1 (83)	>19:1 (79)	>19:1 (60)
3	Bn (**c**)	>19:1 (85)	>19:1 (76)	>19:1 (61)
4	Ph (**d**)	>19:1 (85)	>19:1 (81)	>19:1 (68)

Treatment of enaminedione **1a** with ethylhydrazine gave markedly different results from methylhydrazine at all three temperatures investigated (Table 1, entry 2). However, the regioselectivity at –78 °C was diminished (**2b**/**3b** = 11:1), suggesting at least a slight shift towards **3b**. Both benzyl and phenylhydrazine afforded **2c**,**d** in high regioselectivity irrespective of the temperature (Table 1, entries 3 and 4). The regioisomeric pyrazoles **3c**,**d** were not observed in either crude reaction mixtures or purified products.

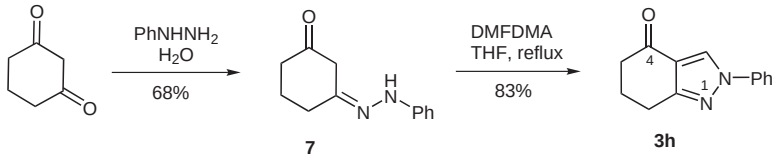
The primary amino group of phenylhydrazine is more nucleophilic than the secondary amino group due to the electron-withdrawing nature of the phenyl ring.[12] Assuming that enaminedione **1a** reacts via the mesomeric structure **4**, one would anticipate the regioselectivity to favor pyrazole **2d** (vide supra). This is in agreement with experimental observations. For alkyl hydrazines one might expect pyrazole **3** to predominate, given that the secondary amino group is the more nucleophilic nitrogen.[13] However, pyrazole **2** is the major product observed experimentally. This observation would suggest that steric effects override any nucleophilic advantage the secondary amino group might possess at temperatures ≥ 0 °C. The reversal in regioselectivity witnessed at –78 °C with methylhydrazine suggests that conditions were favorable for attack by the secondary amino group, or a change in reactivity of **1a** has occurred. For the latter, enaminedione **1a** would react more like **1** than **4**, leading to hydrazone **6**, then ultimately to pyrazole **3a** (Scheme 2).

In general the hydrazinomethylene intermediate **5** was not observed during the course of the reactions, except in the case of R = benzyl where **5** was observed by LCMS (Scheme 2). The presumed conversion of **5** (R = Bn) to **2c** was monitored over the course of several hours at reduced temperatures. The mass corresponding to adduct **6** was not observed for any hydrazine at any temperature.

Since neither **2a** nor **3a** were obtained in adequate regioisomeric excess, it was necessary to develop a scalable separation method. Cycloheptapyrazolone **2a** was crystallized from an enriched mixture of **2a**/**3a** to high regioisomeric excess (>99:1). Similarly, **2a** was precipitated from an enriched mixture of **2a**/**3a** and the filtrate concentrated to afford **3a** in high regioisomeric excess (19:1).

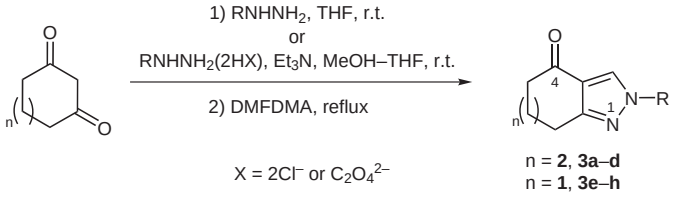
In view of the fact that pyrazole **3** was poorly accessible via enaminedione **1a**, it was necessary to develop an alternate route. It was envisioned that pyrazole **3** might be available by essentially reversing the employment of the same reagents used to synthesize pyrazole **2**. In that, forming a monohydrazone from a substituted hydrazine and a 1,3-dione followed by cyclization with DMFDMA to afford pyrazole **3**. This hypothesis was tested by first generating hydrazone **7** from 1,3-cyclohexanedione and phenylhydrazine.[14] Cyclization to pyrazole **3h** with excess DMFDMA in refluxing THF proceeded in good yield (Scheme 3).

In an attempt to further improve the utility of this synthetic sequence the reaction was performed in a one-pot manner. To this end, 1,3-cyclohexanedione was treated with one equivalent of phenylhydrazine for two hours, then excess DMFDMA was added and the reaction was refluxed overnight (Table 2). Pyrazole **3h** was isolated in 50% yield, which is comparable to the overall yield for the two-



Scheme 3

Table 2 Synthesis of pyrazoles **3a**–**h**[15–18]



Entry	R	n	Pyrazole	Yield (%)
1	Me	2	**3a**	61
2	Et	2	**3b**	52
3	Bn	2	**3c**	47
4	Ph	2	**3d**	48
5	Me	1	**3e**	66
6	Et	1	**3f**	64
7	Bn	1	**3g**	59
8	Ph	1	**3h**	50

step sequence (56%, Scheme 3). The generality of this one-pot reaction was explored using the three other previously employed hydrazines and also examining two different ring sizes (Table 2).[15–17]

The hydrazines and diones investigated provided modest to good yields for the one-pot procedure. In general, the yields for cyclohexanedione (Table 2, entries 5–8) were slightly higher than for cycloheptanedione (Table 2, entries 1–4). Methylhydrazine gave the highest yields for both diones. Ethylhydrazine was comparable in yield to methylhydrazine for cyclohexanedione, but was considerably lower for cycloheptanedione. The two-step reaction sequence seems to be unaffected by the presence of MeOH, $(Et_3NH)^+X^-$, and dimethylamine in this one-pot procedure.

The opposite regioisomers were not observed, with the exception of entry 3.[16] Benzylhydrazine and cycloheptanedione afforded traces of the regioisomeric pyrazole **2c** (25:1 by ^{1}H NMR). Pyrazole **2c** may have arisen through incomplete hydrazone formation, resulting in some remaining benzylhydrazine and cycloheptanedione at the time of DMFDMA addition. Subsequently, DMFDMA can react with cycloheptanedione to form **1a**, which in turn can react with benzylhydrazine to form **2c** (Scheme 3).

In conclusion, a temperature-dependent regioselectivity was observed in the addition of methylhydrazine to enaminedione **1a** to form pyrazoles **2a**/**3a**. It was shown that all other hydrazines examined provided predominantly pyrazole **2**, regardless of temperature. These results prompted the development of a novel one-pot procedure for the synthesis of pyrazoles **3a**–**h** through the in situ generation of the monohydrazone of 1,3-diones and subsequent cyclization with DMFDMA.[19] All pyrazoles described in this manuscript, with the exception of **2d** and **3h**, are previously unreported in the literature.[9b,20,21]

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References and Notes

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attributed to the electrophilicity of the ketone carbonyls (Scheme 1, X = CF_3, Y = CF_3 or aryl), see: (a) Soufyane, M.; Mirand, C.; Levy, J. *Tetrahedron Lett.* **1993**, *34*, 7337. (b) Okada, E.; Masuda, R. *Heterocycles* **1992**, *34*, 791. (c) Also see ref. 2b.

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(7) **Representative Experimental Procedure for Pyrazoles 2a–d**

A solution of 1,3-cycloheptanedione (15.1 g, 120 mmol) in DMFDMA (48 mL, 360 mmol) was heated to reflux for 3 h. The reaction mixture was concentrated at reduced pressure, then dried under high vacuum (3 d, <1 mmHg) until **1a** formed as an amber solid (20.6 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 3.31 (s, 3 H), 2.81 (s, 3 H), 2.62–2.58 (m, 4 H), 1.88–1.85 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.57, 159.94, 113.20, 48,39, 43.61, 40.85, 22.58. HRMS: *m/z* calcd for $C_{10}H_{16}NO_2$ $[M + H]^+$: 182.1181; found: 182.1178.

To a solution of **1a** (507 mg, 2.8 mmol) in MeOH (22 mL) cooled to 0 °C was added a solution of methylhydrazine (164 μL, 3.08 mmol) in MeOH (6 mL) over 5 min. After 1 h the reaction mixture was concentrated in vacuo (**2a**/**3a** = 6:1). Purification by flash chromatography (SiO_2, eluting with 10–20% acetone–CH_2Cl_2) afforded **2a** as a pale-yellow solid (0.355 g, 77%) which was dissolved in warm EtOAc (3 mL), then hexanes (9 mL) was added, and the resulting solution was placed in a –20 °C freezer. The resulting solid was filtered, then dried in vacuo to afford **2a** as small pale-yellow needles (0.278 g); **2a**/**3a** >99:1 by HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 3.79 (s, 3 H), 2.91 (t, *J* = 6.3 Hz, 2 H), 2.71 (t, *J* = 6.1 Hz, 2 H), 2.07–2.02 (m, 2 H), 1.95–1.90 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.58, 145.01, 141.05, 122.69, 44.55, 37.08, 27.41, 25.72, 22.95. HRMS: *m/z* calcd for $C_9H_{13}N_2O$ $[M + H]^+$: 165.1028; found: 165.1029.

Pyrazole **2b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 2.93 (t, *J* = 6.4 Hz, 2 H), 2.71 (t, *J* = 6.1 Hz, 2 H), 2.07–2.02 (m, 2 H), 1.95–1.90 (m, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.13, 143.79, 140.68, 122.78, 44.31, 43.83, 26.43, 25.26, 22.48, 14.89. HRMS: *m/z* calcd for $C_{10}H_{15}N_2O$ $[M + H]^+$: 179.1184; found: 179.1180.

Pyrazole **2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.39–7.25 (m, 3 H), 7.14–7.09 (m, 2 H), 5.30 (s, 2 H), 2.82 (t, *J* = 6.4 Hz, 2 H), 2.82 (t, *J* = 6.1 Hz, 2 H), 1.98–1.92 (m, 2 H), 1.90–1.84 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196,18, 144.75, 141.00, 135.77, 128.91, 122.97, 126.71, 122.82, 53.55, 43.99, 26.78, 25.24, 22.46. HRMS: *m/z* calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$: 241.1341; found: 241.1344.

Pyrazole **2d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.53–7.40 (m, 5 H), 2.96–2.93 (m, 2 H), 2.77–2.75 (m, 2 H), 1.98–1.95 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.26, 145.76, 141.61, 138.85, 129.24, 128.76, 125.67, 123.36, 43.35, 27.26, 25.39, 22.56. HRMS: *m/z* calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$: 227.1184; found: 227.1179.

(8) The identical reaction at 21 °C favored **2a** (**2a**/**3a** = 6:1).

(9) (a) Regioisomer **2** was assigned based on the NOE observed between the R group and the C8 protons (Table 1).
(b) Pyrazole **2d** was found to be identical to that previously described in the literature (see ref. 2a).

(10) (a) All reactions were performed on a 0.5 mmol scale (0.10 M) using 1.1 equiv hydrazine. Reaction conditions are not optimized. (b) Ratio of **2**/**3** from HPLC analysis of crude reaction mixture. (c) Ethylhydrazine oxalate and benzylhydrazine·2HCl were pretreated with Et_3N (2.2 equiv). (d) A solution of the hydrazine was added to a refluxing solution of **1a** for reactions run at elevated temperature.

(11) The identical reaction at 0 °C with methylhydrazine sulfate and Et_3N (2.2 equiv) also favored **2a** (**2a**/**3a** = 5:1).

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(15) **Representative Experimental Procedure for Pyrazoles 3a–h**

(a) Pyrazole **3h**: To a solution of 1,3-cyclohexanedione (112 mg, 1.0 mmol) in THF (4 mL) under argon was added a solution of phenylhydrazine (99 μL, 1.0 mmol) in THF (1 mL) quickly. After 2 h, DMFDMA (402 μL, 3.00 mmol) was added quickly and the resulting solution heated to reflux. After 16 h the reaction mixture was concentrated in vacuo and purified via flash chromatography (12 g SiO_2, 0–60% EtOAc–hexanes) to afford **3h** as an off-white solid (106 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 7.69 (d, *J* = 7.7 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 2.95 (t, *J* = 6.1 Hz, 2 H), 2.57 (t, *J* = 6.6 Hz, 2 H), 2.19 (quin, *J* = 6.3 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.66, 158.08, 139.28, 129.59, 127.65, 126.66, 120.64, 119.73, 38.85, 23.49, 22.99. HRMS: *m/z* calcd for $C_{13}H_{13}N_2O$ $[M + H]^+$: 213.1028; found: 213.1018.

Pyrazole **3a** (pale-yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 3.85 (s, 3 H), 2.97–2.94 (m, 2 H), 2.70–2.67 (m, 2 H), 1.98–1.90 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.28, 153.75, 134.02, 122.83, 43.19, 39.03, 27.79, 25.34, 22.79. HRMS: *m/z* calcd for $C_9H_{13}N_2O$ $[M + H]^+$: 165.1028; found: 165.1023.

Pyrazole **3b** (pale-yellow viscous oil): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1 H), 4.11 (q, *J* = 7.3 Hz, 2 H), 2.99–2.94 (m, 2 H), 2.72–2.67 (m, 2 H), 2.01–1.88 (m, 4 H), 1.49 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.37, 153.45, 132.25, 122.46, 47.12, 43.18, 27.85, 25.32, 22.79, 15.07. HRMS: *m/z* calcd for $C_{10}H_{15}N_2O$ $[M + H]^+$: 179.1184; found: 179.1179.

Pyrazole **3c** (pale-yellow viscous oil): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.39–7.32 (m, 3 H), 7.29–7.23 (m, 2 H), 5.21 (s, 2 H), 3.00–2.94 (m, 2 H), 2.71–2.65 (m, 2 H), 2.00–1.86 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.37, 153.78, 134.93, 133.26, 128.96, 128.51, 128.18, 122.94, 56.20, 43.18, 27.82, 25.29, 22.73. HRMS: *m/z* calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$: 241.1341; found: 241.1334.

Pyrazole **3d** (pale-yellow viscous oil): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 7.68 (d, *J* = 7.7 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.33 (t, *J* = 7.4 Hz, 1 H), 3.10–3.05 (m, 2 H), 2.78–2.73 (m, 2 H), 2.05–1.93 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.46, 154.67, 139.12, 130.42, 129.53, 127.35, 122.62, 119.44, 43.19, 27.82, 25.19, 22.71. HRMS: *m/z* calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$: 227.1184; found: 227.1179.

Pyrazole **3e** (pale-yellow oily solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 3.91 (s, 3 H), 2.83 (t, *J* = 6.3 Hz,

2 H), 2.53–2.46 (m, 2 H), 2.12 (quin, *J* = 6.3 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.44, 157.32, 130.05, 119.25, 39.18, 38.67, 23.62, 22.79. HRMS: *m/z* calcd for $C_8H_{11}N_2O$ $[M + H]^+$: 151.0871; found: 151.0867.
Pyrazole **3f** (pale-yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 2.84 (t, *J* = 6.3 Hz, 2 H), 2.52–2.46 (m, 2 H), 2.13 (quin, *J* = 6.3 Hz, 2 H), 1.51 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.54, 157.09, 128.43, 118.92, 47.38, 38.67, 23.65, 22.86, 15.17. HRMS: *m/z* calcd for $C_9H_{13}N_2O$ $[M + H]^+$: 165.1028; found: 165.1022.
Pyrazole **3g** (pale-yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1 H), 7.39–7.32 (m, 3 H), 7.29–7.24 (m, 2 H), 5.26 (s, 2 H), 2.85 (t, *J* = 6.3 Hz, 2 H), 2.51–2.45 (m, 2 H), 2.12 (quin, *J* = 6.3 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.59, 157.37, 134.83, 129.44, 129.01, 128.58, 128.18, 119.37, 56.43, 38.72, 23.62, 22.89. HRMS: *m/z* calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$: 227.1184; found: 227.1179

(16) The regioisomers of pyrazoles **3e**–**h** were independently synthesized via ref. 1a or 2a.

(17) (a) All reactions were performed on a 1.0 mmol scale (0.20 M) using 1.0 equiv hydrazine and 3.0 equiv DMFDMA. Reaction conditions are not optimized. (b) Ethylhydrazine oxalate and benzylhydrazine dihydrochloride were pretreated with Et_3N (2.2 equiv) for 10 min in MeOH instead of THF due to solubility issues. Otherwise, reactions were run as described in the experimental section.

(18) 1,3-Cycloheptanedione was purchased from Sigma-Aldrich, or when unavailable, synthesized and distilled as described in: Ragan, J. A.; Makowski, T. W.; am Ende, D. J.; Clifford, P. J.; Young, G. R.; Conrad, A. K.; Eisenbeis, S. A. *Org. Process Res. Dev.* **1998**, *2*, 379.

(19) A similar preparation of 3-aryl pyrazoles (Scheme 3) from hydrazone **7** and substituted benzaldehydes has been reported: (a) Teuber, H. J.; Worbs, E.; Cornelius, D. *Chem. Ber.* **1968**, *101*, 3918. (b) Strakova, I.; Strakovs, A.; Petrova, M. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2005**, *41*, 1398.

(20) Pyrazole **3h** has been previously synthesized by a different route: Bajnati, A.; Kokel, B.; Hubert-Habart, M. *Bull. Soc. Chim. Fr.* **1987**, *2*, 318.

(21) Pyrazoles **2a** and **3a** are erroneously reported in Le Tourneau, M. E.; Peet, N. P. US Patent 4734430, **1998**. In example 3 of the patent, pyrazoles **2a** and **3a** are reported as 5,6,7,8-tetrahydro-1-methyl-4(1*H*)-cycloheptapyrazolone and 5,6,7,8-tetrahydro-2-methyl-4(2*H*)-cycloheptapyr-azolone, respectively. However, they should have been reported as 5,6,7,8-tetrahydro-1,3-dimethyl-4(1*H*)-cycloheptapyrazolone and 5,6,7,8-tetrahydro-2,3-dimethyl-4(2*H*)-cycloheptapyrazolone based on the chemistry described therein.