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Highly Regioselective Synthesis of 1-Aryl-3 (or 5)-alkyl/aryl-5 (or 3)-(*N*-cycloamino)pyrazoles

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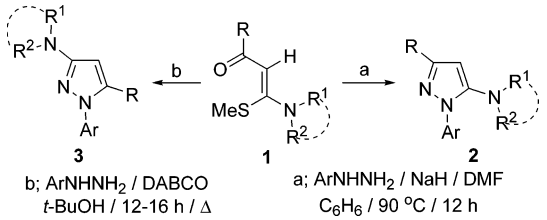
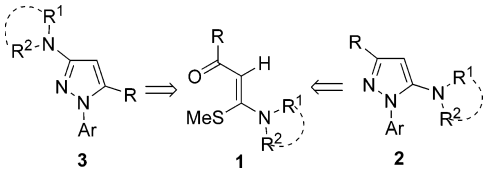


An efficient highly regioselective protocol for the synthesis of isomeric 1,3-diaryl (or 1-aryl-3-alkyl) and 1,5-diaryl (or 1-aryl-5-alkyl)-5 (or 3)-(*N*-cycloamino)pyrazoles has been reported by cyclocondensation of common α-oxoketene *N*,*S*-acetal precursors with arylhydrazines by variation of reaction conditions.

The 1-*N*-arylpyrazole ring system represents an important heterocyclic template that has attracted considerable interest because of its long history of application in pharmaceutical and agrochemical industry.[1] Numerous compounds containing 1-*N*-arylpyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, antiinflammatory, sedative, and hypnotic activities.[1−3] Some of these compounds have emerged as potent and selective γ-aminobutyric acid (GABA)-gated chloride channel antagonists,[2] novel ligands for estrogen receptors,[3] and agrochemicals of economic importance. One of the most important methods for the synthesis of substituted 1-*N*-arylpyrazoles involves cyclocondensation of 1,3-dicarbonyl compounds and their equivalent 1,3-dienophilic synthons such as propargylic ketone, β-dialkylamino/alkoxy/chloroketones with arylhydrazines.[2b,c,3] However the appealing generality of this method is somewhat vitiated as a result of the frequent formation of regioisomeric mixtures of unsymmetrical pyrazoles in these reactions.[3,4] Several elegant methods for the regioselective synthesis of unsymmetrically substituted 1-arylpyrazoles have been developed in recent years;[1c,d,2] however despite their promising potential, these methods have limited applications in terms of generality and offer only little improvement over classical phenylhydrazine-β-diketone route to this class of compounds. Our own interest in addressing this regiochemistry issue stems from our ongoing research program utilizing α-oxoketene dithioacetals as versatile 1,3-electrophilic building blocks for regiospecific synthesis of substituted and condensed five- and six-membered heterocycles and aromatic compounds.[5−7] During the course of these studies, we became interested in probing the reaction of α-oxoketene *N*,*S*-acetals with an unsymmetrical binucleophile such as phenylhydrazine with a view to achieve synthesis of both 5- and 3-amino-1-arylpyrazoles in highly regiocontrolled fashion by variation of reaction conditions (Chart 1). Although several

CHART 1



5-alkyl/arylamino-1-arylpyrazoles have found applications as pharmaceuticals and agrochemical agents exhibiting a range of biological activities, [2,8−10] only a few scattered reports are available on the synthesis of 1-aryl-3-(or 5)-*N*,*N*-disubstituted aminopyrazoles, which are not well represented in the literature.[10] The reported methods for the synthesis of 5-alkyl/arylaminoyrazoles require either harsh reaction conditions[9d,e] or are limited only to a defined set of precursors.[2,9] In a recent report,[10] a few of the substituted 1-aryl-5-(*N*,*N*-disubstituted)aminopy-

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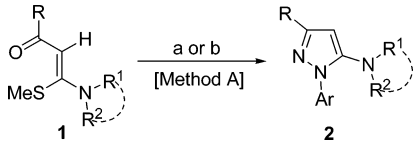
SCHEME 1[a]

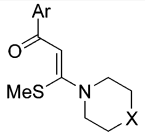
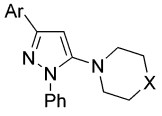
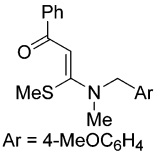
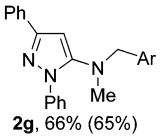
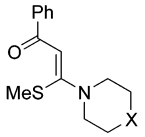
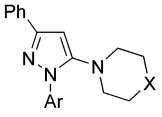
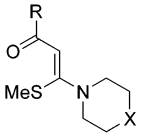
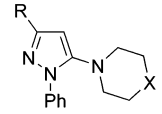


[a] Reagents and conditions: (a) $ArNHNH_2$/NaH/DMF/C_6H_6/90 °C/12 h. (b) $ArNHNH_2$/*t*-BuOK/*t*-BuOH/12 h/Δ.

razoles have been synthesized by treatment of a preformed *N*-arylhydrazones from appropriate β-ketoamides with Lawesson reagent in a one-pot operation. However this protocol has not been extended for the synthesis of 5-(*N*-cycloamino)pyrazoles, whereas the corresponding 3-(*N*-cycloamino)pyrazoles to our knowledge are unknown in the literature. Herein we describe our successful results on regioselective synthesis of substituted 1-aryl-5 (or 3)-*N*-(cycloamino)pyrazoles from common *N*,*S*-acetal precursors.

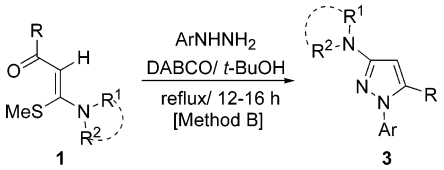
Earlier work from this laboratory has demonstrated synthetic application of α-oxoketene *N*,*S*-acetals as useful three-carbon 1,3-electrophiles in their reactions with symmetrical (hydrazine[11a] and guanidine[11c]) and unsymmetrical (hydroxylamine,[11b] cyanoacetamide,[11d] and lithioaminocrotononitrile[11e]) binucleophiles, yielding the corresponding primary or secondary amino-substituted five- and six-membered heterocycles in highly regioselective fashion.[12] In continuation of these studies, we examined the reaction of ketene *N*,*S*-acetals **1a** with unsymmetrical binucleophile such as phenylhydrazine under varying conditions (mild basic and neutral). In most of the cases, the corresponding 5-(*N*-piperidino)-1,3-diphenylpyrazole (**2a**) was isolated in varying yields, whereas under drastic conditions (neat heating at 120 °C), complex mixtures of products were formed. Under optimized conditions, **2a** was obtained in 77% yield when **1a** was reacted with phenylhydrazine (1.2 equiv) in the presence of sodium hydride in DMF/C_6H_6 at 90 °C (Scheme 1). These reaction conditions were also found to be optimal for the synthesis of 3-(4-methoxyphenyl)-5-(*N*-piperidino)- and the other 5-(*N*-cycloamino)- or the acyclic 5-(*N*-methylbenzylamino)-1,3-diphenylpyrazoles **2b**−**g** in overall high yields (Table 1, entries 2−7). Cycloannulation of the *N*,*S*-acetal **1d** with 4-fluorophenylhydrazine also yielded the corresponding 1-*N*-(4-fluorophenyl)-5-*N*-(piperazino)pyrazole (**4**) in 64% yield (entry 8). The heterocyclization reaction was found to be equally facile with *N*,*S*-acetals **1h**−**j** with aliphatic acyl groups yielding the corresponding 3-alkyl-5-(*N*-cycloamino)pyrazoles **2h**−**j** in good yields (entries 9−11). Similarly the 3-formyl-1-phenyl-5-*N*-(morphilino)-pyrazole **5** was obtained in 61% yield by in situ hydrolysis of the 3-bis(methoxymethyl)pyrazole **2k** obtained from **1k** under identical conditions (entry 12). During the course of this work, we further observed that use of potassium *tert*-butoxide as base in refluxing *tert*-butyl alcohol instead of sodium hydride also gave the 5-aminopyrazoles **2a**−**k** in comparable yields as shown in the Table 1.

TABLE 1. Synthesis of 5-(*N*-Cycloamino)-1-arylpyrazoles

Entry	1	2, 4, 5 (%Yield)[a]
		
1	**1a**, Ar = Ph, X = CH_2	**2a**, 77% (75%)
2	**1b**, Ar = 4-$MeOC_6H_4$; X = CH_2	**2b**, 67% (70%)
3	**1c**, Ar = Ph, X = O	**2c**, 74% (69%)
4	**1d**, Ar = Ph, X = NBn	**2d**, 71% (72%)
5	**1e**, Ar = Ph, X = NCO_2Et	**2e**, 71% (74%)
6	**1f**, Ar = Ph X = N-(2-Pyridyl)	**2f**, 74% (69%)
		
7	**1g**, Ar = 4-$MeOC_6H_4$	**2g**, 66% (65%)
		
8	**1d**, X = NBn, Ar = 4-FC_6H_4	**4**, 64% (68%)
		
9	**1h**, R = Me, X = NBn	**2h**, 70% (73%)
10	**1i**, R = Me X = N-(2-pyridyl)	**2i**, 69% (70%)
11	**1j**, R = *i*-Pr, X = O	**2j**, 71% (71%)
12	**1k**, R = $CH(OMe)_2$; X = O R = CHO; X = O	**2k**[b] **5**, 61%[c] (62%)

[a] Yields obtained from *t*-BuOK are in parentheses. [b] Not isolated. [c] Obtained by in situ acidic hydrolysis of **2k**.

SCHEME 2



After successfully establishing the reaction conditions for obtention of 1-aryl-5-(*N*-cycloamino)pyrazoles **2**, we were further intrigued to develop a general regiocontrolled route for the 1-aryl-5-aryl/alkyl-3-aminopyrazoles (**3**) from the common α-oxoketene *N*,*S*-acetal precursors **1**. Interestingly, we could achieve this goal after several unsuccessful experiments, when **1a** was reacted with phenylhydrazine in the presence of a weaker base such as DABCO (1.2 equiv) furnishing only 3-(*N*-piperidino)-1,5-diphenylpyrazole (**3a**) exclusively in 69% yield with no trace of regioisomeric pyrazole **2a** (Scheme 2, Table 2, entry 1, Method B). The generality of these reaction conditions is evident from the facile synthesis of other isomeric 3-amino-1-aryl-5-aryl/alkylpyrazoles **3b**−**k** parallel to their 5-amino partners **2b**−**k** in good to excellent

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TABLE 2. Synthesis of 3-(*N*-Cycloamino)-1-arylpyrazoles

Entry	1	3, 6, 7 (%Yield)
1	**1a**, Ar = Ph, X = CH_2	**3a**, 69%
2	**1b**, Ar = 4-$MeOC_6H_4$; X = CH_2	**3b**, 64%
3	**1c**, Ar = Ph, X = O	**3c**, 70%
4	**1d**, Ar = Ph, X = NBn	**3d**, 67%
5	**1e**, Ar = Ph, X = NCO_2Et	**3e**, 71%
6	**1f**, Ar = Ph, X = N-(2-Pyridyl)	**3f**, 74%
7	**1g**, Ar = 4-$MeOC_6H_4$	**3g**, 69%
8	**1d**, X = NBn; Ar = 4-FC_6H_4	**6**, 64%
9	**1h**, R = Me, X = NBn	**3h**, 54%
10	**1i**, R = Me, X = N-(2-pyridyl)	**3i**, 68%
11	**1j**, R = *i*-Pr, X = O	**3j**, 80%
12	**1k**, R = $CH(OMe)_2$; X = O R = CHO; X = O	**3k**[a] **7**, 65%[b]

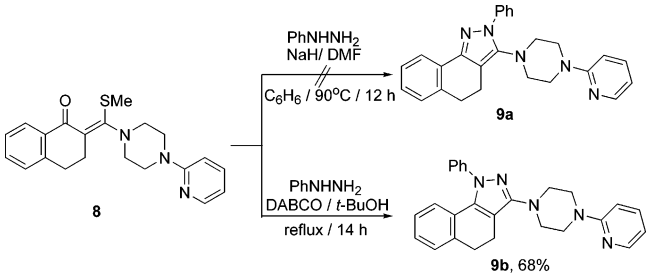
[a] Not isolated. [b] Obtained by in situ acidic hydrolysis of **3k**.

yields as shown in Table 2. The regiochemistry of 5- and 3-(*N*-cycloamino)pyrazoles **2** and **3** was established from the X-ray crystallographic data of one of the regioisomeric pairs **2b** and **3b** (Figures 1 and 2, Supporting Information).

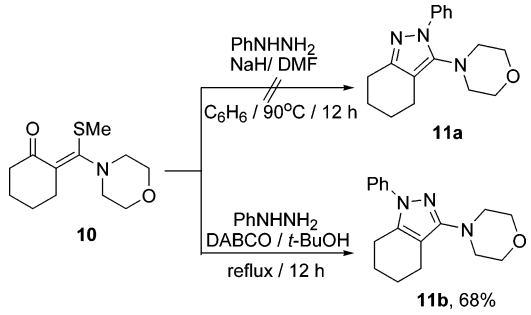
To further extend the scope of this reaction, the *N*,*S*-acetals **8** and **10** derived from cyclic ketones such as tetralone and cyclohexanone, respectively, were reacted with phenylhydrazine under earlier described conditions (Methods A and B) with a view to synthesize regioisomeric 3,4- (**9a**, **11a**) and 4,5- (**9b**, **11b**) annulated 3- (or 5-) aminopyrazoles (Schemes 3 and 4). However, these reactions met with only partial success, yielding the corresponding 3-(*N*-cycloamino)-4,5-annulated pyrazoles **9b** and **11b** in good yields under DABCO-catalyzed conditions (Method B), whereas the reaction of either **8** or **10** with phenylhydrazine in the presence of sodium hydride/DMF or potassium *tert*-butoxide/*tert*-butyl alcohol (Method A) afforded only intractable product mixtures.

The probable mechanism for the formation of the two regioisomeric pyrazoles **2** and **3** from *N*,*S*-acetal **1** in the presence of different bases is shown in Scheme 5. Thus in the presence of a stronger base like sodium hydride

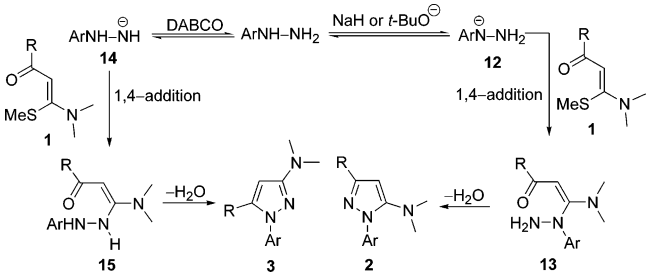
SCHEME 3



SCHEME 4



SCHEME 5



or potassium *tert*-butoxide, the anion **12** is formed by abstraction of more acidic proton of phenylhydrazine.[1a,13] The anion **12** adds to α-oxoketene dithioacetals **1** in 1,4-fashion to give intermediate adduct **13**, which on intramolecular cyclization affords 5-(cycloamino)pyrazole **2**. In the presence of a weaker and sterically crowded base such as DABCO, phenylhydrazine undergoes abstraction of the less hindered NH_2 proton, resulting in the formation of the anion **14**, which undergoes 1,4-addition−elimination with *N*,*S*-acetal **1** to give the intermediate adduct **15**.[14] Subsequent intramolecular cyclization of adduct **15** affords the 3-(cycloamino)pyrazole **3**. Our attempts to trap either of these adducts **13** or **15** were not successful.

The *N*,*S*-acetals **16a,b** carrying a primary amino group were next subjected to cyclization with phenylhydrazine under varying conditions (Scheme 6). Best results were obtained when the reaction of **16a** with phenylhydrazine was effected in the presence of a catalytic amount of acetic acid, yielding the corresponding 5-anilino-1,3-diphenylpyrazole **17a** exclusively in 80% yield. The *N*,*S*-acetal from benzylamine **16b** also furnished the 5-aminopyrazole **17b** in high yield. Our attempts to get

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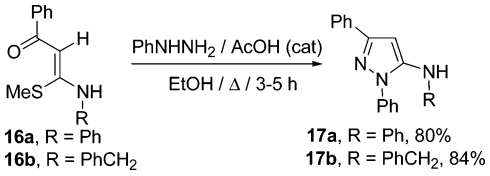
SCHEME 6



3-anilino-5-phenylpyrazole from **16a** under varying conditions were, however, not successful.

In summary, we have developed a highly efficient protocol for the synthesis of 1,3-diaryl (or 1-aryl-3-alkyl) and 1,5-diaryl (or 1-aryl-5-alkyl)-5 (or 3)-(*N*-cycloamino)-pyrazoles from common α-oxoketene-*N*,*S*-acetal precursors in a highly regiocontrolled fashion. Our efforts to extend this regioselective protocol to a wide range of *N*,*S*-acetals derived from various cyclic/heterocyclic ketones and primary amines is currently under progress.

Experimental Section

General details are described in Supporting Information. All known *N*,*S*-acetals **1a**−**k**, **8**, **10**, and **16a**−**b** were prepared by the earlier reported procedure.[11b,12]

General Procedure for Preparation of 1-Aryl-3-aryl/alkyl-5-(*N*-cycloamino)pyrazoles 2, 4. A solution of the respective *N*,*S*-acetal **1** (5 mmol) and arylhydrazine (6 mmol) in benzene (50 mL) was added to a suspension of NaH (0.24 g, 6 mmol) in DMF (10 mL) at room temperature over a period of 0.5 h. The reaction mixture was heated at 90 °C with constant stirring for 12 h (monitored by TLC), poured after cooling into saturated NH_4Cl solution (50 mL), and extracted with benzene (2 × 25 mL). The combined benzene layer was washed with H_2O (3 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and distilled under reduced pressure to give pyrazoles **2** or **4**, which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

1,3-Diphenyl-5-(*N*-piperidino)-1*H*-pyrazole (2a). Yield 77% (1.17 g); pale yellow solid; mp 80−81 °C; R_f 0.80 (9.5:0.5 hexanes−EtOAc). IR (KBr): 3060, 2944, 1593, 1549, 1498, 1450, 1421, 1305, 1256, 1201 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.16−7.23 (m, 2H), 6.09 (s, 1H), 2.79 (t, *J* = 5.4 Hz, 4H), 1.50−1.56 (m, 4H), 1.44−1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 150.7, 140.4, 133.5, 128.7, 128.4, 127.6, 126.2, 125.4, 122.5, 91.4, 52.3, 25.4, 23.8. MS (*m*/*z*, %): 304 (M + 1, 100); 303 (M^+, 90). Anal. Calcd for $C_{20}H_{21}N_3$ (303.40): C, 79.17; H, 6.98; N, 13.85. Found: C, 79.31; H, 6.79; N, 14.01.

General Procedure for Preparation of 1-Aryl-5-aryl/alkyl-3-(*N*-cycloamino)pyrazoles 3, 6. A solution of respective *N*,*S*-acetal **1** (5 mmol), arylhydrazine (6 mmol), and DABCO (0.67 g, 6 mmol) in 50 mL of *t*-BuOH was refluxed for 12−16 h with constant stirring, the reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure and poured into ice-cold water, extracted with DCM (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), and dried over Na_2SO_4. The solvent was evaporated under vacuum to give pyrazoles **3** or **6**, which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

1,5-Diphenyl-3-(*N*-piperidino)-1*H*-pyrazole (3a). Yield 69% (1.05 g); brown solid; mp 105−106 °C; R_f 0.71 (9.5:0.5 hexanes−EtOAc). IR (KBr): 3056, 2930, 1593, 1552, 1512, 1445, 1378, 1348, 1293, 1258, 1236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.04−7.18 (m, 10H), 5.88 (s, 1H), 3.19 (t, *J* = 5.7 Hz, 4H), 1.58−1.63 (m, 4H), 1.46−1.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 143.6, 140.3, 131.1, 128.57, 128.54, 128.2, 127.9, 126.1, 124.7, 95.1, 48.8, 25.3, 24.3. MS (*m*/*z*, %): 304 (M + 1, 90); 303 (M^+, 100). Anal. Calcd for $C_{20}H_{21}N_3$ (303.40): C, 79.17; H, 6.98; N, 13.85. Found: C, 79.27; H, 7.05; N, 13.63.

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Supporting Information Available: ^1H and ^{13}C NMR spectral data for compounds and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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