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Facile Scalable Reduction of *N*-Acylated Dihydropyrazoles

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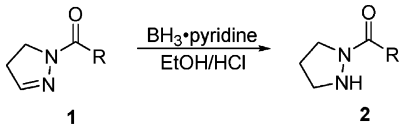


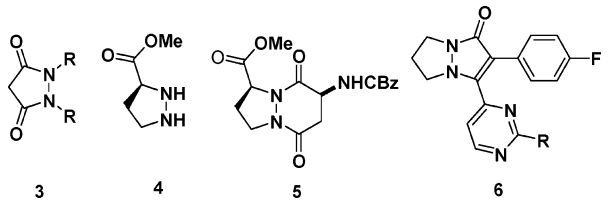
1 **2**

12 unique examples reported

The reduction of a variety of highly functionalized *N*-acylated dihydropyrazoles (**1**) with BH_3•pyridine is described. The process through which this unexpectedly difficult reduction was discovered and developed is reported. A facile atom-efficient route to the *N*-acylated dihydropyrazole reduction precursors (**1**) is also illustrated. The resulting acylpyrazolidine products (**2**) that arise upon reduction were isolated in good to high yields following exposure to reaction conditions which have been shown to tolerate a variety of different functional groups. Finally, this route has been demonstrated on a kilogram scale and provides direct access to potential proline surrogates for peptidomimetic applications.

The significance of the pyrazolidine heterocycle is evidenced by its presence as a structural subunit in a variety of compounds frequently utilized in both the photography and pharmaceutical industries.[1−7] The photography industry has employed pyrazolidinediones (**3**) as the main component in both pigments as well as thermal-based printing materials (Scheme 1).[1] Furthermore, pyrazolidine compounds have been converted into azaproline amino acids (**4**), which have been studied upon incorporation into traditional peptides as well as small molecule peptidomimetics (**5**).[2−6] Our interest in this heterocycle stems from its presence as a key pharmacophore in a series of

SCHEME 1

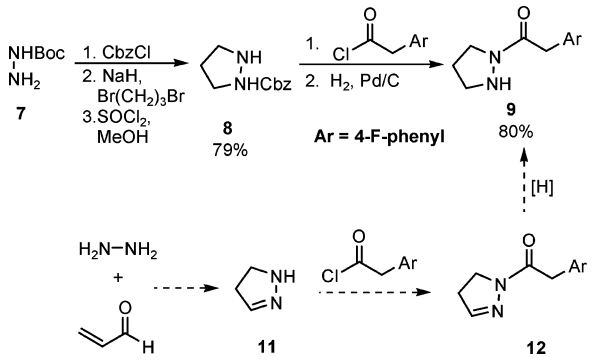


3 **4** **5** **6**

pyrazolone-based compounds (**6**) which have been shown to be potent inhibitors of cytokines, namely tumor necrosis factor-α (TNF-α).[7]

Several methods have been reported for constructing this key pyrazolidine pharmacophore including dipolar cycloaddition techniques as well as the linear protocol employing the orthogonal protecting group strategy depicted in Scheme 2 (**7**−**9**).[7−11] While this latter route was certainly capable of producing gram quantities to supply early studies in the development of the pyrazolone-based drug candidates (**6**), a method capable of quickly producing multiple-kilogram quantities of this key intermediate was required to supply additional studies.

SCHEME 2



7 **8** 79% **Ar = 4-F-phenyl** **9** 80%

11 **12**

One potential shorter alternative route to this key intermediate **9** was recognized which originates with the condensation of hydrazine and acrolein to provide the dihydropyrazole (**11**) (Scheme 2).[12,13] Acylation of **11** with the requisite acid chloride followed by reduction of cyclic hydrazone (**12**) would quickly open up access to the acylpyrazolidine (**9**) in an atom-efficient fashion.

The synthesis of **11** from hydrazine and acrolein has been previously described in the literature.[12,13] However, these methods are complicated by both the instability and water solubility of **11**, which hinder its isolation or require specialized equipment to effect this transformation neat in the vapor phase.

A viable short synthetic process to **9** was developed which circumvented the stability and water solubility problems inherent

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(2) Lecoq, A.; Boussard, G.; Marraud, M. *Tetrahedron Lett.* **1992**, *33*, 5209−5212.
(3) Zhang, W.-J.; Berglund, A.; Kao, J. L−F.; Couty, J.-P.; Gershengorm, M. C.; Marshall, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 1221−1235.
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(6) Kim, H.-O.; Lum, C.; Lee, M. S. *Tetrahedron Lett.* **1997**, *38*, 4935−4938.
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(8) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193-2196.
(9) Barluenga, J.; Fernandez-Mari, F.; Viado, A. L.; Aguilar, E.; Olano, B.; Garcia-Granda, S.; Moya-Rubiera, C. *Chem. Eur. J.* **1999**, *5*, 883−896.
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(11) Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379−8380.
(12) Heinemann, U.; Thomas, R.; Lantzsch, L.; Ditgens, K.; Weber, E. U.S. Patent 4 434 292, 1984.
(13) Engel, P. S.; Bodager, G. A. *J. Org. Chem.* **1988**, *53*, 4748−4758.

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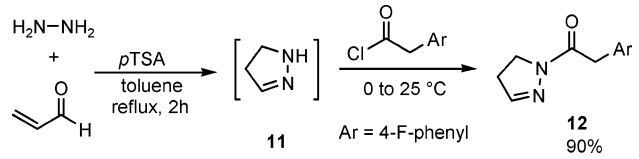
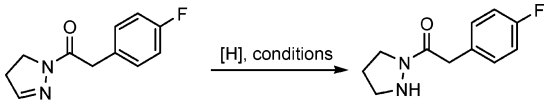
SCHEME 3



to **11** (Scheme 3). This was accomplished by generating the dihydropyrazole (**11**) from hydrazine and acrolein in the presence of catalytic pTSA, whereupon the resulting water was removed by azeotropic distillation. The remaining product-laden toluene solution was then treated with 4-fluorophenylacetyl chloride to form **12** in high reproducible yield in a single reaction pot. With **12** in hand, its subsequent reduction to the desired acylpyrazolidine (**9**) turned out to be far more difficult than originally anticipated.

Few reports have been published that describe the reduction of acylated dihydropyrazoles analogous to **12**.[9−11] Carreira and co-workers reported one of the closest related examples by employing $NaCNBH_3$ in AcOH.[10,11] While this method appeared to be promising during in situ monitoring, the isolation of **9** in high purity and yield proved to be problematic (Table 1, entry 1). Upon further experimentation, it was found that a strong acid (HCl) and polar solvent (DMF) were critical to drive this reaction to completion and obtain high product yield (entry 2). However, these conditions proved to be far too hazardous to consider applying on kilogram scale due to both the incompatibility of $NaCNBH_3$ and DMF as well as the constant liberation of HCN gas due to the harsh acidic conditions required to effect the reaction.[14]

TABLE 1. Survey of Reducing Agents for 12

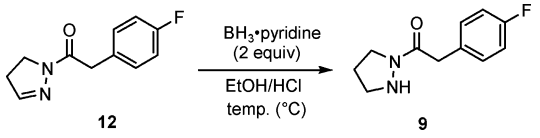


entry	[H] source	solvent	*T* (°C)	ratio **9**/**12**[a]	**9** (% yield)
1	$NaCNBH_3$	AcOH	25	>95:5	60
2	$NaCNBH_3$	DMF/HCl	25	98:2	80
3	BH_3·pyridine	EtOH/HCl	25	32:68	40
4	$NaBH_4$	MeOH	25	70:30	34[b]
5	$LiAlH_4$	MeOH	0	over-reduction	
6	DIBALH	THF	−78	over-reduction	
7	K-Selectride	THF	−78	over-reduction	
8	H_2 (Pd/C, Pt/C)	MeOH/HCl	25−50	66:34	

[a] Ratios estimated using HPLC peak areas to assess the consumption of **12** and formation of **9** solely as a qualitative measure due to significant extinction coefficient differences between each. [b] Cleavage of the pyrazole ring was observed as *p*-fluorophenethyl alcohol was isolated.

Other traditional hydride-based reducing agents were also screened. BH_3·pyridine initially only gave a small amount of the desired reduced product (Table 1, entry 3). Several other reducing agents, such as $NaBH_4$, $LiAlH_4$, DIBALH, and K-Selectride, all gave complicated reaction mixtures likely due to competing over-reduction reaction pathways (Table 1, entries 4−7). The over-reduced products originated from the partial or complete reduction of the amide carbonyl. Further complicating the use of these traditional reducing agents was their incompatibility with the harsh acidic conditions required to push the reaction to completion. Finally, the hydrogenation of **12** was investigated at varying pressures (40−90 psi), temperatures (25−50 °C), and acid additives with both Pd- and Pt-based catalysts without complete success (Table 1, entry 8).

TABLE 2. Optimization of BH_3·Pyridine Reduction Conditions



entry	HCl (equiv)	*T* (°C)	ratio **9**/**12**[a]	**9** (% yield)
1	1	0	<5:95	
2	1	20	32:68	
3	1	40	32:68	
4	1	60	32:68	
5	0	20	<1:99	
6	1	0−20	32:68	
7	2	0−20	67:33	
8	3	0−20	89:11	
9	4	0−20	96:4	75[b]

[a] Ratios determined at 3 h reaction time using HPLC peak areas corrected for differences in the extinction coefficients of **9** and **12**. [b] Demonstrated on a multi-kilogram (3 kg) scale over three runs.

Closer examination of the reaction profile for the BH_3·pyridine reduction conditions (Table 1, entry 3) revealed the greatest potential development opportunity. The HPLC profile of this reaction indicated it was very clean and perhaps more importantly, significant unreacted BH_3·pyridine remained suggesting that the reaction was "stalled" out. As a result, both the effect of temperature and the amount of acid employed in the reaction were investigated to determine if either would promote the reaction to completion (Table 2.).

A survey of the temperature dependence of the reduction was carried out at temperatures ranging from 0 to 60 °C (Table 2, entries 1−4). The only temperature effect that was observed for this reduction was found between 0 and 20 °C where the reduction only occurred as the reaction approached ambient temperature. At temperatures greater than ambient, no dependence of the reduction on the reaction temperature was observed.

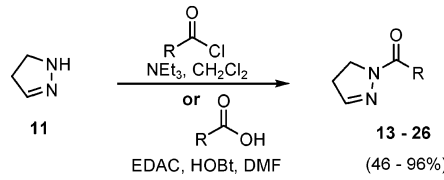
The criticality of acid on the reduction was revealed while investigating the reaction's dependence over 0−4 equiv of HCl (Table 2). The reaction does not proceed without any acid, and the amount of reduction product increases as the amount of acid employed is increased incrementally up to 4 equiv. With 4 equiv of acid and 2 equiv of BH_3·pyridine, the acylpyrazolidine product was isolated in 75% yield (entry 9).

The dependence of the reduction reaction on excess acid and BH_3·pyridine can be attributed to the competing decomposition pathway of the reducing agent under the harsh acidic environment required to effect the reaction. This is directly evidenced by the hydrogen off-gassing that is observed as the reaction progresses to completion.

While this reduction method met our needs to quickly access kilogram quantities of the acylpyrazolidine (**9**) to support the development of the pyrazolone-based drug candidates (**6**), the general applicability of the method to a broad range of functionalized substrates was unknown. Toward this end, a wide range of *N*-acylated dihydropyrazoles were synthesized according to one of two traditional methods based on the commercial

(14) The incompatibility of $NaCNBH_3$ with DMF was revealed on an adiabatic temperature screen of the reaction mixture and falls in line with other observed hydride/DMF incompatibilities (see: *Chem. Eng. News* **1982**, *60*, 5, 43.).

SCHEME 4



availability of the corresponding acylating agent (Scheme 4).[15] The corresponding acylated dihydropyrazoles **13**−**26** were obtained in 46−96% yield.

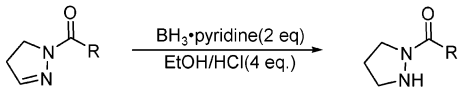
The reduction precursors selected to illustrate the functional group tolerance of the method were chosen on the basis of their likely incompatibility with other conventional reduction conditions (Table 3). A variety of *N*-acylated dihydropyrazoles possessing conjugated and nonconjugated olefins, aromatic esters, nitriles, bromides, and nitroaromatic functionalities have been found to be tolerant of the reduction conditions as illustrated in Table 3. For example, reduction of the *N*-3-oxopropionic acid derivative (**13**) provided the reduction product **27** in moderate yield (entry 1). Reduction of dihydropyrazoles containing either conjugated or nonconjugated double bonds provides the corresponding reduced acylpyrazolidine products in a wide range of yields (entries 2−5). The variable nature of product yields obtained upon reduction of these olefinic substrates was investigated by increasing the substitution of the carbon−carbon double bond. While trans-disubstituted *N*-methacrylate substrate **14** gave a low yield (31%, entry 2), increasing the substitution at the β position doubles the yield of the corresponding reduced product **29** (entry 3). However, the increased substitution of the olefin is not the only contributing factor to the low yield encountered on reduction of **14** as the reduction of the *N*-cinnamyl substrate **17** gave 99% yield of the reduced product **31**. We propose that the propensity of the methacrylate functional group to polymerize is a main contributing factor to the low yield encountered with **14**.

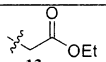
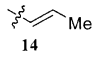
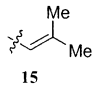
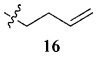
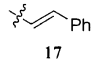
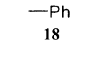
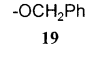
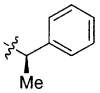
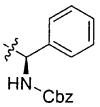
The reduction of a variety of electronically diverse *N*-aryl-acylated dihydropyrazoles (**18**−**26**) proceeded smoothly with yields ranging from 58 to 99%. The reaction conditions were shown to be highly tolerant of aromatic bromides, esters, nitriles, and nitroaromatic functional groups, providing the corresponding reduced products in good yields (entries 8−11). An electronic dependence of the aromatic ring does not appear to exist for this reduction as the reduction of **24** with an electron-donating *p*-methoxy group gave the pyrazolidine (**38**) in 69% yield.

Finally, the ability of the reduction conditions to conserve the stereointegrity of enantiomerically enriched reduction precursors was investigated using **25** and **26** (entries 13 and 14). While the reduction of these two substrates proceeded in high yields, partial racemization of the reduction products was observed under these reaction conditions.

In summary, we have developed a BH_3·pyridine reduction method for a variety of functionalized *N*-acylated dihydropyrazoles which proceeds in good to high yield and has been shown to be applicable at kilogram scale. While this method has been shown to tolerate a wide range of functional groups, it is unable to conserve the stereointegrity of the two enantiopure substrates investigated.

TABLE 3. Functional Group Compatibility Survey for BH_3·Pyridine Reduction Conditions



Entry	Pyrazole (-R)[a]	Product	Isolated Yield[b]
1	 **13**	**27**	48%
2	 **14**	**28**	31%
3	 **15**	**29**	61%
4	 **16**	**30**	63%
5	 **17**	**31**	99%
6	 **18**	**32**	58%
7	 **19**	**33**	88%
8	*p*-BrPh (**20**)	**34**	99%
9	*p*-NO_2Ph (**21**)	**35**	94%
10	*p*-CNPh (**22**)	**36**	72%
11	*p*-CO_2MePh (**23**)	**37**	89%
12	*p*-OMePh (**24**)	**38**	69%
13	 **25** (>99:1 er)	**39**	97% (80:20 er)[c]
14	 **26** (>99:1 er)	**40**	98% (87:13 er)[c]

[a] See the Supporting Information for the preparation and characterization of the pyrazoles. [b] Isolated yield is reported for analytically pure material. [c] Enantiomeric purity was established by comparison with the corresponding racemates using chiral stationary phase HPLC.

Experimental Section

General Representative BH_3·Pyridine Reduction Procedure. At room temperature, a nitrogen inerted reaction vessel was charged with the *N*-acyldihydropyrazole and ethanol (10 mL/g relative to the dihydropyrazole). To the homogeneous substrate mixture was added borane·pyridine complex (2 equiv) in a single portion. The

(15) The dihydropyrazole (**11**) used to synthesize the reduction precursors to illustrate functional group compatibility of the reduction method was obtained in gram quantities from TCI Chemicals.

(16) An, D. K.; Kim, H.-M.; Kim, M. S.; Kang, S. K.; Ha, J. D.; Kim, S. S.; Choi, J.-K.; Hun, J. H. *Heterocycles* **2004**, *63*, 2379.

reaction was then cooled to 0 °C, at which time a solution consisting of 50% 6 N HCl (4 equiv) in ethanol was added to the reaction over 40 min maintaining the internal reaction temperature <15 °C. Following the addition, the reaction was gradually warmed to 20 °C over 30 min when the reaction was noted complete by TLC and was subsequently cooled to 10 °C. The reaction was quenched by the addition of 6 N HCl (3 equiv) over 10 min followed by water (5 mL/g relative to the dihydropyrazole) over ~15 min. The pH of the reaction mixture was adjusted using 6 N NaOH to bring the pH from 0.84 to 8.7. The reaction mixture was extracted with ethyl acetate. The combined organic portions were then washed with water and saturated NaCl solution, and dried over $MgSO_4$. The $MgSO_4$ was then filtered, and the product rich filtrate was then concentrated under reduced pressure. The filtrate was azeotroped with heptanes to remove any remaining pyridine.

Acknowledgment. We are grateful to Mr. David Berry for creating the HPLC methods used to develop this reduction method along with Mr. Dennis Billings who led the effort to demonstrate this method on a kilogram scale.

Supporting Information Available: Full characterization and experimental procedures, including analytical methods, for **13**−**26** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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