JOC Article

Room Temperature ICl-Induced Dehydration/Iodination of 1-Acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles. A Selective Route to Substituted 1-Acyl-4-iodo-1*H*-pyrazoles

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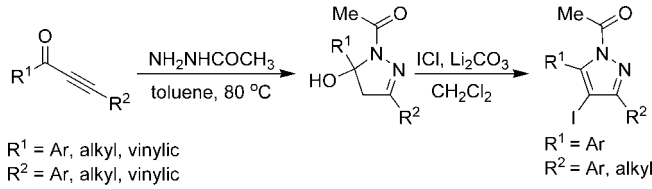
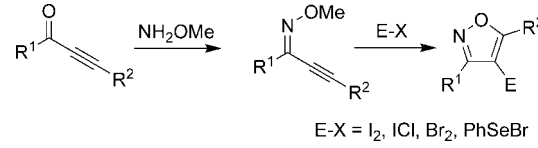


A number of new functionally substituted 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been prepared in moderate to excellent yields from the corresponding 2-alkyn-1-ones. The resulting dihydropyrazoles undergo dehydration and iodination in the presence of ICl and Li_2CO_3 at room temperature to provide 1-acyl-4-iodo-1*H*-pyrazoles.

Introduction

Pyrazoles and derivatives have attracted considerable attention due to the wide variety of biological activities they exhibit, including hypoglycemic, antimicrobial, amoebicidal, antibacterial, anti-inflammatory, antipyretic, and analgesic activities.[1] Specifically, 5-hydroxy-4,5-dihydro-1*H*-pyrazoles are known to possess anti-inflammatory and analgesic activity.[2] Pyrazoles exhibit analgesic,[3] antimicrobial,[4] anti-inflammatory,[5] antihypertensive,[6] and hypoglycemic[7] activities, and appear promising as potential antiprotozoal and cytotoxic agents,[8] and CB1 cannabinoid receptor antagonists as appetite suppressants for the treatment of obesity.[9] Even today, the pyrazole core continues to emerge as a central candidate for pharmaceutical and agricultural applications.[10]

SCHEME 1



We recently reported the synthesis of highly substituted isoxazoles by the electrophilic cyclization of 2-alkyn-1-one *O*-methyl oximes (Scheme 1).[11] The requisite ynone *O*-methyl

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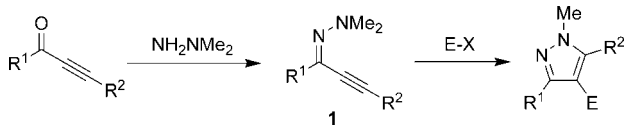
SCHEME 2



oximes were prepared by stirring the ynone in the presence of methoxylamine hydrochloride, pyridine, and Na_2SO_4 or $MgSO_4$ at room temperature with methanol as the solvent.[12]

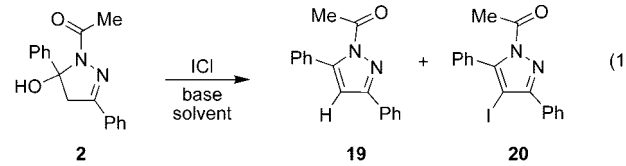
We reasoned that an analogous synthetic strategy could be applied toward the synthesis of highly substituted pyrazoles. We envisioned that 2-alkyn-1-one *N*,*N*-dimethylhydrazones (**1**) would react in the presence of an electrophile to afford substituted 1-methylpyrazoles (Scheme 2). However, this synthetic strategy was unsuccessful, because we were unable to prepare the requisite hydrazones, and thus an alternative route to 4-halopyrazoles was ultimately developed. We wish herein to report our results on that project.

Results and Discussion

The preparation of dimethylhydrazones, such as **1**, is not as straightforward as was first anticipated. Our attempts at the preparation of dimethylhydrazones, such as **1**, by 1,2-addition of 1,1-dimethylhydrazine to alkynones or by metal−acetylide additions to hydrazonyl halides did not lead to any desired products. In addition, copper- and palladium-catalyzed cross-coupling reactions of terminal acetylenes with hydrazonyl halides failed to provide the anticipated dimethylhyrazones. Discouraged by the inability to readily prepare such dimethylhydrazones for subsequent electrophilic cyclization to pyrazoles, we developed an alternate methodology.

When acyl and aroyl hydrazine derivatives were first allowed to react with alkynones, the products were originally assigned an open chain form.[13] Since then, their structures have been reassigned and a small number of 5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been reported by the reaction of hydrazine derivatives with alkynones.[13] To the best of our knowledge, the analogous reaction with acetylhydrazine has not been reported. 5-Hydroxy-4,5-dihydro-1*H*-pyrazoles have also been prepared by the reaction of hydrazine derivatives with 3-alkoxy-alk-2-en-1-ones.[14] The synthesis of 5-hydroxy-4,5-dihydro-1*H*-pyrazoles from alkynones is attractive due to the many ways one can selectively synthesize alkynones from commercially available starting materials.[15]

A literature search revealed that iodine has been used as a Lewis acid for the facile dehydration of aldoximes to nitriles.[16] We envisioned that the dehydration of *N*-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles, followed by iodination, could provide a selective route to substituted 1-acyl-4-pyrazoles. Thus, we synthesized 1-acetyl-5-hydroxy-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (**2**) as the model system for optimization of this process. The use of I_2 and carbonate bases, such as K_2CO_3, Li_2CO_3, and Na_2CO_3, in CH_2Cl_2 or CH_3CN provided no reaction of **2**. We then shifted our attention to the use of ICl. ICl has been established as the most Lewis acidic of the halogens.[17] We were pleased to find that 1.2 equiv of ICl in the presence of 2 equiv of Na_2CO_3 in CH_2Cl_2 provided complete conversion of **2** to the corresponding 1-acetyl-3,5-diphenyl-1*H*-pyrazole (**19**) (60% yield) and 1-acetyl-4-iodo-3,5-diphenyl-1*H*-pyrazole (**20**) (30% yield) (eq 1).



(1)

To increase the solubility of the inorganic base, CH_3CN and $MeNO_2$ were screened as solvents under the same reaction conditions. However, this provided messy reaction mixtures and provided none of the desired product. Among carbonate bases screened, using CH_2Cl_2 as the solvent in the presence of ICl, Li_2CO_3 provided the best results. The use of Li_2CO_3 nearly reversed the product ratio, compared with Na_2CO_3, providing a 13% yield of **19** and a 52% yield of **20**, although the reaction took two days to reach completion. Omitting Li_2CO_3 from the reaction led to the formation of deacylated pyrazole products, presumably due to the formation of HCl. The optimal reaction conditions thus far developed involve stirring 0.25 mmol of the dihydropyrazole **2**, 3 equiv of ICl, and 2 equiv of Li_2CO_3 in 2.5 mL of CH_2Cl_2 at room temperature, which affords a 95% yield of **20**.

With optimized conditions in hand, we synthesized a number of 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles from the corresponding 2-alkyn-1-ones (Table 1). In most cases, preparation of the 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles proceeded smoothly in good yield by simply heating the appropriate alkynone in the presence of 2 equiv of acetylhydrazine in toluene at 80 °C. When R^1 is a phenyl group, the reaction proceeds satisfactorily in most cases. Both the parent system and one containing an electron-deficient aryl group gave the desired dihydropyrazoles **2** and **3** in good yields (Table 1, entries 1 and 2). Substituting an *n*-butyl group on the terminus of the alkyne moiety was also tolerated well and provided **4** in a good yield (Table 1, entry 3). Only when R^2 = 1-cyclohexenyl did the reaction afford only a modest yield of compound **5** (Table 1, entry 4).

When the 1 position of the 2-alkyn-1-one was substituted with a 2-naphthyl group, the reaction gave a yield of **6** comparable to that of the parent system (Table 1, compare entries 1 and 5). Halogens in the para position of the aromatic ring, including F, Cl, Br, and trifluoromethyl, provided good yields of the desired 5-hydroxy-4,5-dihydro-1*H*-pyrazoles **7**, **8**, **9**, and **10**, respectively (Table 1, entries 6−9). The presence of an electron-withdrawing cyano group in the para position also gave a good yield of **11** (Table 1, entry 10). Electron-rich aryl groups, including *p*-*t*-Bu, 3,4-OCH_2CH_2O−, and 3,4,5-trimethoxy phenyl groups also worked well and provided good

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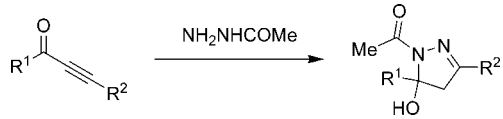
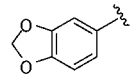
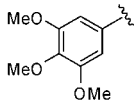
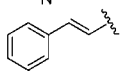
TABLE 1. Synthesis of 1-Acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles[a]



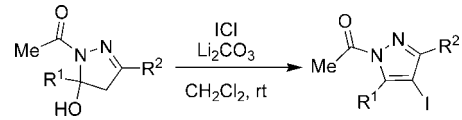
entry	R^1	R^2	product	yield (%)[b]
1	Ph	Ph	**2**	77
2	Ph	*p*-$EtO_2CC_6H_4$	**3**	86
3	Ph	*n*-Bu	**4**	60
4	Ph		**5**	47
5	2-naphthyl	Ph	**6**	79
6	*p*-FC_6H_4	Ph	**7**	95
7	*p*-ClC_6H_4	Ph	**8**	78[c]
8	*p*-BrC_6H_4	Ph	**9**	72
9	*p*-$CF_3C_6H_4$	Ph	**10**	96
10	*p*-NCC_6H_4	Ph	**11**	71
11	*p*-*t*-BuC_6H_4	Ph	**12**	65
12		Ph	**13**	71
13		CH_3	**14**	78
14	*p*-$Me_2NC_6H_4$	Ph	**15**	53[d]
15	*o*-MeC_6H_4	Ph	**16**	64[d]
16		Ph	**17**	93
17		Ph	**18**	68

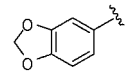
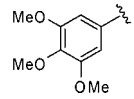
[a] All reactions were carried out using 1.0 mmol of alkynone, 2.0 mmol of acetylhydrazine in toluene (5 mL) at 80 °C for 6 h unless otherwise specified. [b] Isolated yields after column chromatography. [c] X-ray crystallographic data are available for this compound in the Supporting Information. [d] The reaction required 24 h to reach completion.

yields of **12**, **13**, and **14**, respectively (Table 1, entries 11−13). The highly electron-rich benzene ring containing a *p*-Me_2N group provided only a modest yield of **15** and the reaction required a 4-fold increase in reaction time (Table 1, entry 14). A methyl group in the ortho position of the benzene ring provided a slightly lower yield of **16** and required a longer reaction time compared to that of the parent system (Table 1, compare entries 1 and 15). A 3-pyridyl substituent provided an excellent yield of **17** (Table 1, entry 16). The reaction also tolerated a vinylic group in the R^1 position, affording cinnamyl derivative **18** (Table 1, entry 17). Thus, this approach to 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles appears to be quite general.

With the desired 1-acetyl-5-hydroxy-4,5-dihydropyrazole derivatives in hand, we studied the scope of the ICl-induced dehydration/iodination process (Table 2). Under our optimized

TABLE 2. Synthesis of 1-Acetyl-4-iodopyrazoles[a]



entry	R^1	R^2	time (h)	product	yield (%)[b]
1	Ph	Ph	0.75	**20**	95
2	Ph	*p*-$EtO_2CC_6H_4$	1	**21**	75
3	Ph	*n*-Bu	0.75	**22**	97
4	Ph		0.75	**23**	37[c]
5	2-naphthyl	Ph	0.75	**24**	96
6	*p*-FC_6H_4	Ph	1	**25**	84
7	*p*-ClC_6H_4	Ph	1	**26**	87[d]
8	*p*-BrC_6H_4	Ph	1	**27**	82
9	*p*-$CF_3C_6H_4$	Ph	1	**28**	71
10	*p*-NCC_6H_4	Ph	12	**29**	56[e]
11	*p*-*t*-BuC_6H_4	Ph	1	**30**	90
12		Ph	1	**31**	93
13	*o*-MeC_6H_4	Ph	12	**32**	60[f]
14	*p*-$Me_2NC_6H_4$	Ph	24		0
15		Ph	24		0
16		CH_3	12	**33**	41[f]

[a] Unless otherwise stated, all reactions were carried out in CH_2Cl_2 (10 mL/mmol) at room temperature with 2.0 equiv of Li_2CO_3 and 3.0 equiv of ICl. [b] Isolated yields after column chromatography. [c] Yield determined by NMR spectroscopy. [d] X-ray crystallographic data are available for this compound in the Supporting Information. [e] Four equiv of ICl was used. [f] Yield determined by NMR spectroscopy. Nonhalogenated pyrazole is the major side product.

conditions, pyrazole **20** was obtained in an excellent yield (Table 2, entry 1). Substitution of the phenyl ring in the R^2 group by an electron-withdrawing CO_2Et group afforded a slightly lower yield of **21** as compared to the parent system (Table 2, compare entries 1 and 2). Replacing the aryl moiety with an alkyl group also led to the desired pyrazole **22** in an excellent yield (Table 2, entry 3). Unfortunately, introducing a vinylic group in the R^2 position led to only a low yield of the desired pyrazole **23** (Table 2, entry 4). Pyrazole **23** was observed by ^{1}H NMR spectroscopy. However, inseparable impurities alongside the product could not be removed by column chromatography. The lower yield may be attributed to the generation of HCl in the reaction mixture, which may cause unwanted side reactions with the 1-cyclohexenyl group or perhaps the ICl is reacting directly with the carbon−carbon double bond.

We have also studied the effect of varying the nature of the R^1 group, while retaining R^2 as a phenyl group. When R^1 is a 2-naphthyl group, the reaction proceeded smoothly and gave an excellent yield of the pyrazole **24**, which is comparable to the yield of the parent system (Table 2, compare entries 1 and 5). Phenyl groups bearing an F, Cl, or Br in the 4-position all provided the corresponding 4-iodopyrazoles **25**, **26**, and **27**, respectively, in good yields (Table 2, entries 6−8). The structure of compound **26** has been confirmed by X-ray analysis. The presence of a CF_3 group in the 4-position of the aromatic ring also provided the desired 4-iodopyrazole **28** in a good yield (Table 2, entry 9). Introducing an electron-withdrawing CN group into the 4-position of the phenyl group of R^1 provided only a modest yield of 4-iodopyrazole **29** and a dramatic increase in the required reaction time was noted (Table 2, entry 10). Increasing the amount of ICl only provided a modest increase in yield and the results were within experimental error. Electron-rich aromatic rings, including 4-*t*-BuC_6H_4 and 3,4-methylenedioxyphenyl, provided good yields of **30** and **31**, respectively (Table 2, entries 11 and 12). To examine the effect of steric bulk on the benzene ring, we employed compound **16** under our optimized reaction conditions. The reaction proceeded, although an increased reaction time was required and only a moderate yield of **32** was obtained. Unfortunately, **32** could not be separated from its nonhalogenated counterpart (Table 2, entry 13). When R^1 was a *p*-$Me_2NC_6H_4$ or 3-pyridyl group, the reaction provided none of the desired 4-iodopyrazoles (Table 2, entries 14 and 15). Despite employing 10 equiv of ICl, **17** failed to react. This observation may be a result of the basic nitrogen atoms tying up the Lewis acidic ICl, preventing it from effecting the desired dehydration reaction. Additional equivalents of ICl were not attempted in the case of compound **15** because of the likelihood of an unwanted side reaction caused by iodination of the *p*-$Me_2NC_6H_4$ moiety through electrophilic aromatic substitution. Compound **14** was subjected to our dehydration conditions to study the effect of an electron-rich ring in the R^1 position and a sterically compact group in the R^2 position. This reaction suffered from extended reaction times and the corresponding pyrazole, minus an iodine moiety, was detected as the major side product by ^{1}H NMR spectroscopy, along with 4-iodopyrazole **33** (Table 2, entry 16).

The advantage of this methodology is that 1-acyl-4-iodo-3,5-disubstituted-1*H*-pyrazoles can be synthesized selectively from the corresponding alkynones under mild reaction conditions. To the best of our knowledge, the iodination of 1-acylpyrazoles has not been reported, although bromination has.[18] Aryl iodides generally react more readily than their bromine counterparts in the presence of palladium catalysts due to more facile oxidative addition.[19] 1-Acyl-4-halopyrazoles have demonstrated their importance as intermediates for palladium-catalyzed Sonogashira cross-coupling reactions leading to compounds of pharmacological interest.[20] Also, the palladium-catalyzed Heck[21] cross-coupling of 1-acyl-4-halopyrazoles has been demonstrated. In addition, another advantage of this methodology is the fact that the acylation of pyrazoles often gives a mixture of *N*-acylated products,[22] leading to unwanted and often inseparable product mixtures, where our process eliminates this problem. We believe that this approach to substituted pyrazoles should be quite useful in synthesis, considering the many ways one can transform the resulting iodine functional group by catalytic methods other than those described above.

Conclusions

A number of new 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been synthesized in good to excellent yields from 2-alkyn-1-ones. 3,5-Disubstituted-1-acyl-4-iodo-1*H*-pyrazoles have been synthesized in moderate to excellent yields by a novel dehydration/iodination of 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles under mild reaction conditions. Our methodology is fairly general and provides a selective route to 1-acyl-4-iodopyrazoles. To the best of our knowledge, this is the first report of an ICl-induced dehydration of a heterocyclic derivative that provides iodinated pyrazoles.

Experimental Section

General Procedure for Preparation of the 1-Acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles. The alkynone (1.0 mmol) and acetylhydrazine (2.0 mmol, 148.2 mg) in toluene (5 mL) were heated to 80 °C with stirring. The reaction was monitored by TLC until the reaction was complete. The solution was concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel with CH_2Cl_2/EtOAc as the eluent.

1-Acetyl-5-hydroxy-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (2). Purification by flash chromatography (15:1 CH_2Cl_2/EtOAc) afforded 194 mg (77%) of the product as a colorless solid: mp 139−141 °C; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.44 (s, 1H), 3.33−3.39 (d, J = 18.3 Hz, 1H), 3.67−3.73 (d, J = 18.2 Hz, 1H), 5.12 (s, 1H), 7.29−7.43 (m, 8H), 7.69−7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.5, 50.7, 94.0, 124.1, 126.8, 128.4, 129.0, 130.7, 131.4, 144.0, 152.8, 171.1 (1 peak missing due to overlap); HRMS calcd for $C_{17}H_{16}N_2O_2$ 280.1212, found 280.1221.

General Procedure for Dehydration/Iodination of 1-Acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles with ICl. The appropriate 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (0.25 mmol) and finely powdered Li_2CO_3 (0.5 mmol) in CH_2Cl_2 (2.5 mL) were allowed to stir vigorously for 5 min at room temperature. To the vigorously stirred slurry, in the absence of light, was slowly added a freshly prepared solution of ICl (1 M in CH_2Cl_2, 3.0 equiv) and the solution was allowed to stir at room temperature. The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated

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under vacuum to yield the crude product, which was purified by flash chromatography on silica gel with hexanes/EtOAc as the eluent.

1-Acetyl-4-iodo-3,5-diphenyl-1*H*-pyrazole (20). Purification by flash chromatography (9:1 hexanes/EtOAc) afforded 92.2 mg (95%) of the product as an off-white solid: mp 86−88 °C; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.75 (s, 3H), 7.34−7.38 (dd, J = 3.8, 7.4 Hz, 2H), 7.44−7.53 (m, 6H), 7.90−7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.1, 71.7, 128.4, 128.6, 128.9, 129.4, 129.5, 129.8, 131.4, 131.9, 148.1, 154.3, 169.4; HRMS calcd for $C_{17}H_{13}IN_2O$ 388.0073, found 388.0085.

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Supporting Information Available: Characterization of previously unknown starting materials and final products, including full ^{1}H and ^{13}C NMR spectra, and the X-ray structures of compounds **8** and **26**, including CIF files and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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