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Microwave Synthesis of 1-Aryl-1*H*-pyrazole-5-amines

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Abstract

A microwave-mediated synthesis of 1*H*-pyrazole-5-amines utilizing 1M HCl at 150 °C was developed in order to provide products in a matter of minutes with minimal purification. Most reactions are complete in only 10 minutes and can be isolated *via* a simple filtration without the need for further purification by column chromatography or recrystallization. This method tolerates a range of functional groups and can be performed on milligram to gram scales.

Keywords

Pyrazole-5-amines; Microwave; Heterocycles; Green Chemistry

Introduction

1-Aryl-1*H*-pyrazole-5-amines are reoccurring scaffolds and building blocks in a number of biologically active compounds. Since their initial characterization,[1] 1-aryl-1*H*-pyrazole-5-amines have appeared in pesticides,[2] antimicrobials,[3] kinase inhibitors,[4] antileishmanial agents[5] and chemotherapy candidates.[6] Given their wide utility, a number of procedures have been developed to prepare these compounds. A popular modern synthetic method involves the extended reflux of an aryl hydrazine and 3-aminocrotonitrile in either acidic aqueous or alcoholic solutions,[7] followed by purification *via* chromatography and/or recrystallization. α-Cyanoketones can be used in place of 3-aminocrotonitrile to generate a variety of 1-aryl-1*H*-pyrazole-5-amines with additional substitutions at the 3-position. A number of reaction conditions have been reported for this method as well, including heating at reflux for an extended period in toluene,[8]

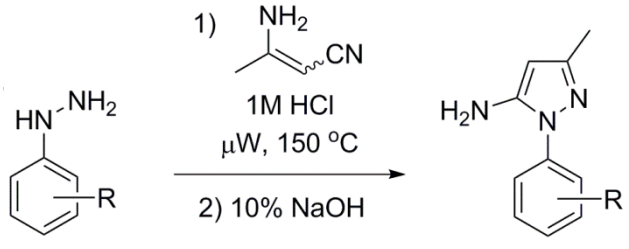
alcohols[9] and polyethylene glycol,[10] yielding product after purification *via* extraction and/or chromatography.

Our group became interested in the preparation of a variety of 1-aryl-1*H*-pyrazole-5-amines for use in building more complex compounds as a part of our antimalarial studies. Given the limited number of commercially available derivatives and the fact that we wished to prepare compounds that were not reported in the literature, we sought to develop a method that could produce 1-aryl-1*H*-pyrazole-5-amines in a quick, efficient manner with little or no required purification. We recently reported our successful development of a microwave mediated procedure for the rapid synthesis of β-carbolines,[11] and we thought that a similar method could be developed for pyrazole-5-amines. The literature contains a few references describing the use of a microwave to prepare pyrazole-5-amines, but these reported methods have a number of drawbacks. One report details the use of a conventional microwave utilizing toluene as a solvent.[12] This method requires several hours of heating, likely due to the fact that toluene is known to be fairly transparent to microwave radiation, and offers little advantage to conventional heating. Another paper detailed the use of methanol as the solvent, but again required long reaction times and produced high reaction pressures.[13] One additional paper reported the use of ethanol as the solvent, but only reported a single compound and found that a full 4h of heating were required, again offering little acceleration versus conventional heating methods.[14]

Results and Discussion

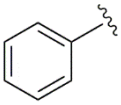
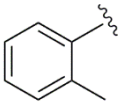
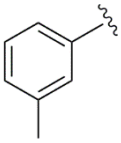
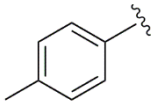
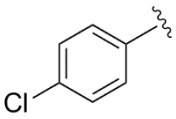
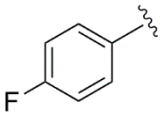
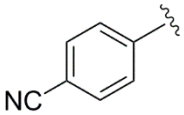
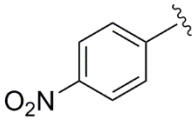
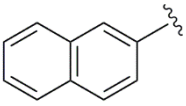
We decided to examine utilizing water as a solvent in the microwave given its status as a "green" reagent, the fact that it readily absorbs microwave radiation, and its wide use in a number of synthetic applications.[15] We also reasoned that the product could be easily isolated from the aqueous solution *via* addition of sufficient base to make the solution alkaline. We first tested our hypothesis by reacting 3-aminocrotonitrile with a variety of commercially available arylhydrazines, and were pleased to find that a 1M HCl solution at 150 °C provides clean product for substrates in a matter of minutes (Table 1). Most products were easily isolated by making the reaction solution alkaline with 10% NaOH, then filtering to obtain the product in excellent purity. In cases where no precipitation was observed, the product was instead isolated with a liquid-liquid extraction using dichloromethane (**1b** and **1c**). All products had excellent purity as indicated by NMR spectroscopy and required no further purification by chromatography or recrystallization (see ESI).

Table 1. Synthesis of *N*-aryl substituted 1*H*-pyrazole-5-amines from 3-aminocrotonitrile.



1a-i

Entry	R	Product	Time[a] (min)	Isolated Yield (%)

1		**1a**	10	84
2[b]		**1b**	10	90
3[b]		**1c**	10	77
4[c]		**1d**	10	92
5		**1e**	10	82
6		**1f**	10	69
7		**1g**	15	73
8		**1h**	10	72
9		**1i**	10	66

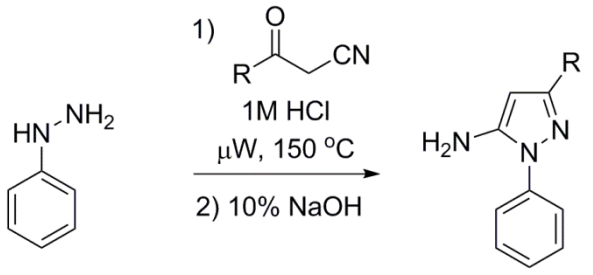
[a]Indicated by TLC. [b]Extracted with CH_2Cl_2. [c]1.5g scale.

We found that 1M HCl was the optimal concentration of acid for use with this procedure, as higher concentrations of HCl provided no significant acceleration of the observed reaction times, while much lower concentrations of HCl caused solubility issues with some substrates. We also found that a temperature of 150 °C gave sufficiently short reaction times, while avoiding degradation of starting reagents and maintaining vessel pressures below 10 bar. While higher temperatures can certainly be used for some substrates, we prefer to always keep operating pressures below 10 bar as a matter of safety. Interestingly, we found that the heterocycle 4-hydrazinopyridine failed to provide product, with ^{1}H-NMR spectroscopy indicating a complex mixture of by-products. However, our method did tolerate a number of other functional groups,

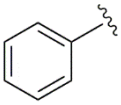
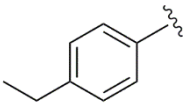
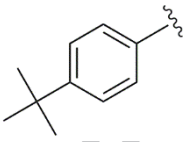
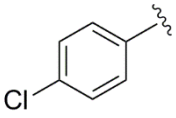
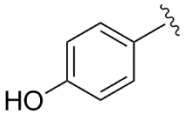
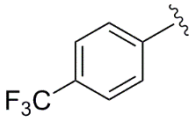
including alkyl, halogen, nitrile and nitro groups. We also found that our conditions worked on both the milligram and gram scale, as we were able to prepare compound **1d** on both the milligram and gram scale with no apparent change in observed reaction times or yields.

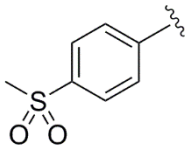
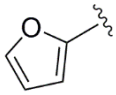
Next, we turned our attention to introducing more complex substituents at the 3-position by using α-cyanoketones. We prepared the desired α-cyanoketones from their respective brominated precursors following a previously published procedure,[16] then combined them with phenylhydrazine under the same conditions used above (Table 2).

Table 2. Synthesis of 1*H*-pyrazole-5-amines from α-cyanoketones.



2a-i

Entry	R	Product	Time[a] (min)	Isolated Yield (%)
1		**2a**	10	78
2		**2b**	10	87
3		**2c**	10	96
4		**2d**	10	79
5[b]		**2e**	10	76
6		**2f**	10	94

7		**2g**	35	74
8[c]		**2h**	20	84
9		**2i**	10	89

[a]Indicated by TLC. [b]Made alkaline with $NaHCO_3$. [c]Extracted with CH_2Cl_2.

Most substrates tested provided products in moderate to excellent yields after only 10 minutes of irradiation, with two compounds requiring slightly longer reaction times (**2g** and **2h**). Interestingly, we found that both *m*-nitrophenyl and *p*-nitrophenyl-3-oxopropanenitrile failed to fully react with phenylhydrazine, even after more than 2.5h of heating. However, our reaction conditions did tolerate a number of other functionalized aromatic groups including a trifluoromethyl group and a methyl sulfone. We were also able to readily isolate a *p*-hydroxyphenyl derivative (**2e**) by utilizing sodium bicarbonate instead of sodium hydroxide in the isolation step. Our conditions also tolerated a 2-furanyl heterocycle, as well as a *tert*-butyl substituent. All compounds were precipitated and isolated *via* a simple filtration in excellent purity with the exception of the 2-furanyl derivative, which was isolated by a liquid-liquid extraction with CH_2Cl_2.

Conclusion

The microwave reaction of arylhydrazines with 3-aminocrotonitrile at 150 °C in 1M HCl readily provides 1*H*-pyrazole-5-amines in 10-15 minutes, with most products isolated in moderate to excellent yields after a simple filtration. The use of α-cyanoketones with phenylhydrazine under the same conditions also yields a number of functionalized 1*H*-pyrazole-5-amines in a matter of minutes. A total of 18 compounds were prepared with yields ranging from 66-96%, with isolated product masses ranging from the milligram to gram scale. All isolated compounds were of excellent purity by NMR and required no chromatography or recrystallization. This procedure is significantly faster than other reported procedures, and most substrates only require aqueous solutions during reaction and isolation. This procedure also tolerates a broad range of functional groups, including halides, nitriles, phenols, sulfones and various alkyl-substituted aromatic rings.

Acknowledgements

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Supporting Information

Supplementary data including synthetic procedures and characterization data for all reported compounds can be found at (INSERT WEB ADDRESS HERE)

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Highlights

- Pyrazole-5-amines appear in molecules with a diverse range of activities
- A microwave-mediated method was developed to produce products in minutes
- Products can be isolated with a simple filtration using only water as the solvent