Alumina-Promoted Synthesis of N-Aryl-1,2,4-Triazoles from Substituted Hydrazines and Imides

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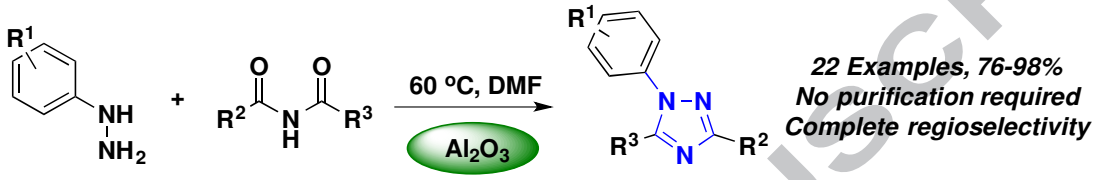

22 Examples, 76-98%
No purification required
Complete regioselectivity

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Alumina-Promoted Synthesis of N-Aryl-1,2,4-Triazoles from Substituted Hydrazines and Imides

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Department of Chemistry and Biochemistry, Rowan University, 201 Mullica Hill Rd., Glassboro, NJ, 08028, USA

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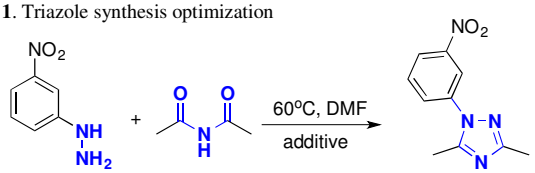
ABSTRACT

Herein we report the highly efficient, environmentally friendly alumina-promoted synthesis of *N*-aryl-1,2,4-triazoles with a wide variety of substitution patterns from commercially available hydrazines with symmetrical and unsymmetrical imides. Aromatic hydrazines with a variety of substitution patterns provided the corresponding 1,2,4-triazoles in very high yields. Unsymmetrical imides with a wide variety of functional groups also provide the respective triazoles with high yield and complete regioselectivities. The high productivity and mild conditions allow for the large-scale preparation of 1,2,4-triazoles.

1,2,4-Triazoles are a distinctive class of nitrogen-containing heterocycles with a wide variety of pharmacological properties.[1] They are highly recurrent in many natural products and commercial drugs.[2] This scaffold has been a key focus in multiple therapeutics, including anticancer, antibacterial, antifungal, antimicrobial, antiviral, antidepressant, anticonvulsant, anti-inflammatory, and central nervous system modulators.[3] Substituted 1,2,4-triazoles have also been applied in pesticides, functional materials, and as ligands in catalysis.[4] Based on the high importance of this scaffold, the development of methods for its synthesis has been a focus in organic chemistry.[5] Most of the available methods entail approaches with low efficiencies and harsh reaction conditions.[6] Recently, Nagasawa reported that nitriles and amidines undergo oxidative cyclizations to provide the respective triazoles.[7] A more recent report has shown that nitriles and hydroxylamine can also form 1,2,4-trilazoles.[8] These contributions are novel, but they still lack generality and overall efficiency. Thus, the development of simplified, more efficient, and cost effective methods for the synthesis of 1,2,4-triazoles remains a goal in the chemistry community.

This laboratory is focused on developing efficient and green methods for the synthesis of pharmacologically relevant nitrogen-containing heterocycles.[9] Herein we report the direct reaction of substituted hydrazines and imides under mild conditions for the efficient synthesis of the proposed triazoles. Symmetrical and unsymmetrical imides are easily accessible synthons through several synthetic methods.[10] Thus, this approach would allow access to a wide variety of 1,2,4-triazoles with diverse substitution patterns.

Table 1. Triazole synthesis optimization



triazole ***1***

Entry	Stoichiometry[a]	Solvent	Additive	Temperature	Yield[b]
1	1:1	Ethyl Lactate	TiO_2	90 ºC	26%
2	1:1	Toluene	TiO_2	90 ºC	25%
3	1:1	DMF	TiO_2	40 ºC	53%
4	1:1	DMF	TiO_2	90 ºC	33%
5	1:1	Tartaric Acid /DMU	TiO_2	90 ºC	66%
6	1:1	DMF	TiO_2/Al_2O_3[c]	40 ºC	78%
7	1:2	DMF	Al_2O_3[d]	60 ºC	88%
8	1:2	EtOAc	Al_2O_3[d]	60 ºC	25%
9	1:2	$CHCl_3$	Al_2O_3[d]	60 ºC	41%
10	1:2	Acetonitrile	Al_2O_3[d]	60 ºC	31%

a. Hydrazine:diacetamide. *b.*Isolated yields. *c.* Neutral alumina.
d. Basic alumina.

This study began by assessing classical conditions to initiate condensation between hydrazines and carbonyl derivatives (**Table 1**). However, most of these required extremely high heat or high concentrations of strong acids or bases.[11]

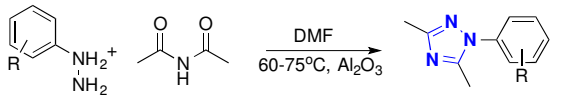
The initial concept for this reaction estimated that strong polar media and a highly oxophilic additive would efficiently promote the desired transformation. Moreover, similar studies have shown that rutile (TiO_2) can act as a mild and efficient promoter for some organic transformations.[12] The proposed reaction in ethyl lactate and TiO_2 unfortunately was only able to provide the desired triazoles in 26% yield (Entry 1). Other solvents at different temperatures were found to provide the expected triazole in moderate yields (Entries 2-4). Moreover, Brønsted acid media (tartaric acid/DMU mixture) allowed for the isolated yield to rise to 66% with almost complete conversion (Entry 5). The attention turned to other metal oxides as potential promoters for this reaction, unfortunately without improving the formation of the desired triazoles.[13] On the other hand, neutral alumina in combination with TiO_2 at 40 °C provided triazole **1** in 78% yield (Entry 6). Moreover, basic alumina in DMF at 60 °C with hydrazine in excess provided triazole **1** in considerably higher yield (88%, entry 7). The results with EtOAc, $CHCl_3$, and acetonitrile provided significantly lower yields (Entries 8-10). The optimization efforts for the synthesis of triazole **1** showed that in DMF at 60 °C followed by filtration through Al_2O_3 yields are very high and required no purification.

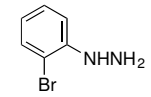
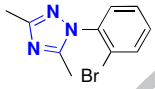
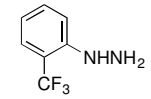
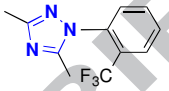
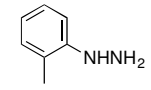
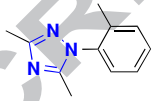
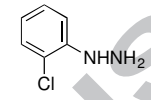
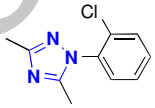
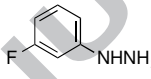
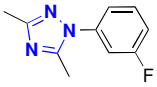
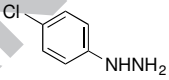
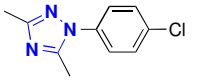
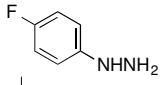
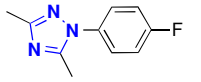
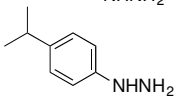
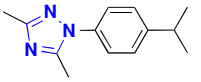
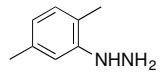
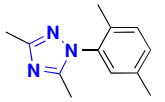
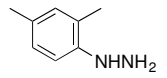
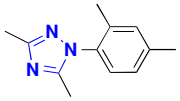
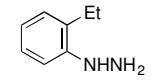
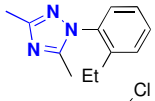
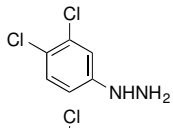
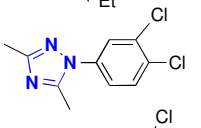
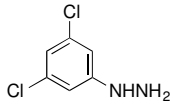
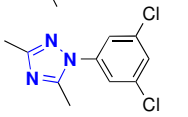
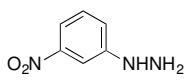
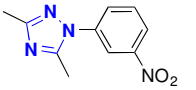
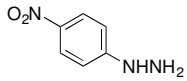
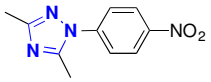
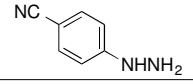
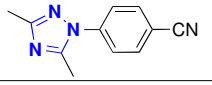
Having identified the optimized conditions, we then focused on studying the scope of this reaction for aromatic hydrazines. This laboratory is dedicated to developing efficient methods for the synthesis of nitrogen-containing heterocycles. Thus, this approach would allow access to a wide variety of 1,2,4-triazoles with diverse substitution patterns (**Table 2).**

The scope study initially focused on assessing the effect of monosubstituted phenylhydrazines. The results showed that *o*-bromo-phenyl hydrazine provided the respective triazole in very high yield (Entry 1). Similarly, *o*-trifluoromethyl and o-methyl were successful at producing the expected triazoles (Entries 2 and 3). Moreover, *o*-chloro and *m*-fluoro phenyl hydrazine provided the proposed triazoles in equally high yields (Entries 4 and 5). Phenylhydrazines with halogens in the *para* position were also suitable substrates for this reaction. Thus, *p*-chloro and *p*-fluoro phenylhydrazines displayed great conversions and yields for this reaction (Entries 6 and 7). There was a concern that *para* activated phenylhydrazines would trigger side reactions and eventually require difficult purifications. Successful efforts found that *p*-isopropyl, 2,6-dimethyl, 2,4-dimethyl, and *o*-ethyl provided the respective triazoles in excellent yields without traces of side products (Entries 8-11). The focus then turned towards highly deactivated phenylhydrazines. It was found that 3,4-dichloro, 3,5-dichloro phenylhydrazines were successful at providing the respective triazoles without any purification step (Entries 12 and 13). Moreover, *m*-nitro, *p*-fluoro, and *p*-cyano phenylhydrazines were also successful at providing the expected product in high yields without evidence of side reactions (Entries 14-16).

The large hydrazine scope for this reaction encouraged us to look into exploring the efficiency against unsymmetrical imides. Several reports have described the synthesis of these molecules. However, it was found that only by reacting aromatic nitriles with alkyl anhydrides in the presence of PTSA at 80 °C the imide was formed. These efforts were able to produce a large array of unsymmetrical imides in significant yields.[10c] The interest mostly lay in unsymmetrical imides with significantly different electronic and steric properties. Thus, we anticipated that *N*-acetyl benzamides would react in high regioselectivity for the predicted triazole **(Table 3).**

Table 2 Reaction scope for hydrazines

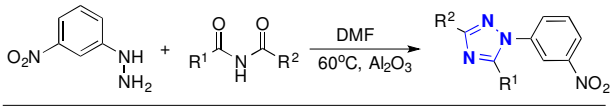


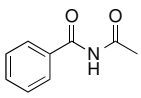
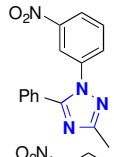
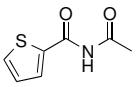
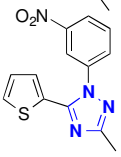
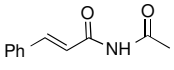
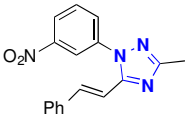
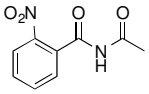
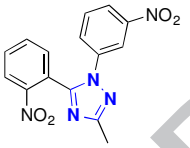
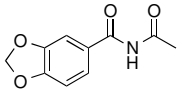
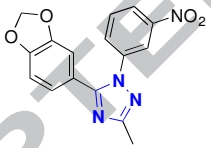
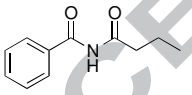
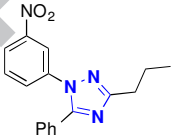
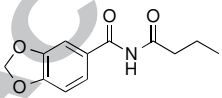
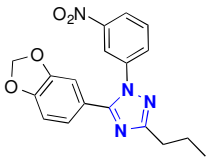
Entry[a]	Hydrazine	Triazole	Yield[b,c]
1			86%[c]
2			78%[c]
3			82%[c]
4			99%
5			78%
6			90%
7			77%
8			90%
9			97%
10			99%
11			96%
12			99%
13			91%[c]
14			88%
15			86%[c]
16			92%[c]

a. Reaction conditions: Hydrazine (0.2 mmol), diacetamide (0.1 mmol) in DMF at 60 °C for 12h, then filtered through Al_2O_3 (1 g).
b. Isolated without silica gel column chromatography purification.
c. Reactions were ran in 500 mg of scale.

The scope for unsymmetrical imides began by reacting *N*-acetylbenzamide with *m*-nitro phenylhydrazine under the optimized conditions and the results showed that the triazole scaffold was successfully isolated as a single isomer (Entry 1). Then, it was found that *N*-acetylthiophene-2-carboxamide and *N*-acetylcinnamide reacted with high efficiencies to provide the expected triazoles (Entries 2 and 3).

Table 3 Reaction Scope for Imides

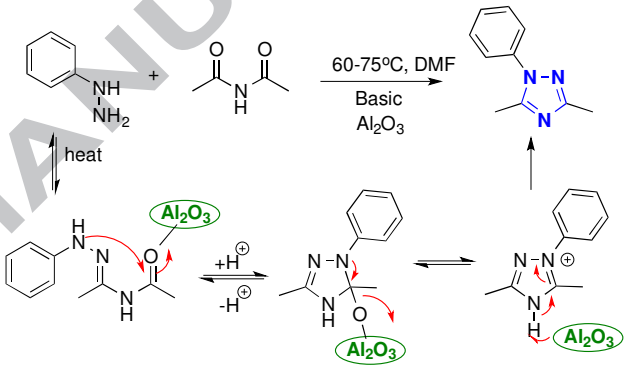


Entry[a]	Imide	Triazole[b]	Yield[c]
1			83%
2			81%
3			94%
4			47%
5			95%
6			87%
7			93%

a. Reaction conditions: Hydrazine (0.2 mmol), imide (0.1 mmol) in DMF at 60 °C for 12h, then filtered through Al_2O_3 (1 g).
b. Regioselectivity was determined by NOESY.
c. Isolated without silica gel column chromatography purification.

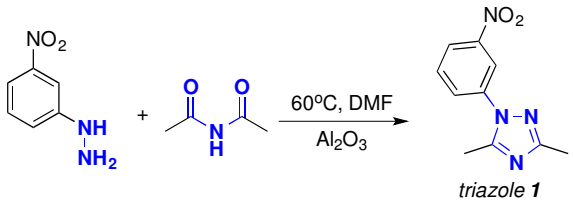
There was also interest in assessing the effect of substituents on the benzamide group. The results showed that deactivated *N*-acyl *o*-nitrobenzamide reacted with slightly lower yield (Entry 4). Despite the lower yield, no other triazole scaffold was isolated. On the other hand, activated *N*-acylpiperonylamide provided the triazole in very good yield (Entry 5). Similar high yields were found with *N*-butyryl benzamides (Entries 6 and 7). Complete selectivity for the 1,5-regioisomer was observed and the high regioselectivity was rationalized due to the hydrazine preference for the electrophilic acetyl group on the imide substrate. These results were confirmed by NOESY experiments on the resulting triazoles (SI).

This study was also concerned with obtaining a better understanding of the reaction mechanism for this transformation (**Scheme 1**). Initial assessment of the effect of Al_2O_3 found that heating the substrates in DMF at 60 °C in the absence of alumina provided *N*-acetyl amidrazone as the only organic product.[14] Thus, it was hypothesized that upon initial condensation between the hydrazine and the imide, the corresponding amidrazone undergoes alumina-promoted intramolecular cyclization to ultimately provide the observed triazole. Metal oxides have been reported to promote condensation pathways for the synthesis of heterocyclic scaffolds.[15] This effect can be rationalized due to the aluminium oxide (32-63 microns) strong surface lattice interactions with the *N*-acetyl amidrazone intermediate; thus promoting the triazole-forming step.



Scheme 1 Proposed 1,2,4-triazole synthesis mechanism

Lastly, the attention shifted towards determining the green properties of this method. We were interested in assessing the recyclability and scalability of this reaction (**Scheme 2**). The recyclability for the reaction was assessed through five consecutive 20 mmol reactions using the same Al_2O_3 batch, which was recovered after each filtration.



	Cycle 1[a]	Cycle 2	Cycle 3	Cycle 4	Cycle 5
Yield of **1**[b]	84%	82%	86%	89%	85%

a. Hydrazine (40 mmol), diacetamide (20 mmol) in DMF(10 mL) at 60 °C for 12h, then filtered through Al_2O_3 (10 g) and then washed with EtOAc (40 mL). *b.* Isolated yield after solvent evaporation.

Scheme 2. Reaction promoter recyclability study

The results displayed high yields for the formation of triazole **1** after each cycle without erosion in conversion or purity. The

efficiency, minimal use of organic solvents, recyclability, and scalability of this method highlights its potential application in large-scale 1,2,4-triazole manufacturing.

In summary, we have developed a highly efficient alumina-promoted synthesis of substituted *N*-aryl-1,2,4-triazoles from hydrazines and easily accessible imides. The mild reaction conditions allow for this method to tolerate a large array of functional groups with diverse electronic and steric properties. Additionally, all of the reaction products were isolated without the need of complicated purifications. In the case of unsymmetrical imides the reaction preceded with complete regioselectivity. The proposed mechanism logically validates the dramatic effect observed with alumina. The reaction can be efficiently scaled-up and the promoter can be reused without affecting the reaction yield. Future efforts will focus on further understanding this reaction for the construction of more structurally diverse triazoles and other nitrogen-containing heterocycles.

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Notes and references

[§] Department of Chemistry and Biochemistry, Rowan University, 201 Mullica Hill Rd, Glassboro, New Jersey, USA. E-mail: **moura-letts@rowan.edu**

Electronic Supplementary Information (ESI) available: [Experimental protocols and spectroscopic data for each triazole are provided].

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