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Acid-catalyzed reaction of 4-methyl-1,2,4-triazoline-3,5-dione (MeTAD) with substituted benzenes

Gary W. Breton *

Berry College, Department of Chemistry, PO Box 495016, Mount Berry, GA 30149, United States

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ABSTRACT

The reaction of 4-methyl-1,2,4-triazoline-3,5-dione (MeTAD) with substituted benzenes under the influence of trifluoroacetic acid catalysis was investigated. Generally, good-to-high yields of 1-arylurazoles resulting from aromatic substitution were obtained. Successful reaction required moderately electron-rich aromatics with proper substitution patterns. The reaction was tolerant of functionality on the aromatic ring.

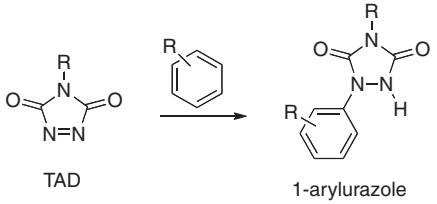
4-Alkyl and 4-aryl-1,2,4-triazoline-3,5-diones (TADs) are potent azo compound electrophiles. The reactions of TADs with alkenes and dienes, as well as many other functional groups, have been rigorously studied.[1] However, only spurious investigations on the reactions of TADs with substituted benzenes have been reported.[2–8] In most cases, TADs react to give 1-arylurazoles, that is, products expected from an electrophilic substitution reaction (see Scheme 1).

1-Arylurazoles have potential pharmaceutical applications as vasodilators, anticonvulsants, and analgesics.[9–11] In addition, oxidation of 1-arylurazoles gives rise to an interesting class of persistent cyclic hydrazyl radicals.[12] Given the potential usefulness of 1-arylurazole compounds, the development of novel strategies toward the synthesis of these compounds is warranted. Therefore, we initiated a systematic study of the reactivity of 4-methyl-1,2,4-triazoline-3,5-dione (MeTAD, i.e., Scheme 1 where R = Me) with a series of aromatic compounds under acid-catalyzed conditions. MeTAD was selected as the TAD substrate since its immediate precursor (the *N*-methylurazole) is commercially available, and the characteristic *N*-methyl signal in the ^{1}H NMR spectrum (generally ranging from ~2.8 to 3.3 ppm) provides a convenient spectroscopic tag for the determination of product distributions in crude reaction mixtures.

Thermal reactions of TADs with electron-rich benzenes, such as 1,3,5-trimethoxybenzene,[7] substituted phenols,[2,4] and dimethyl aniline[5] to afford the corresponding 1-arylurazoles have been reported in the literature in a series of unconnected publications. The success of these reactions was dependent on the presence of sufficiently strong electron-donor groups on the benzene ring. For example, we observed that while reaction between 1,3,5-trimethoxybenzene and MeTAD in CH_2Cl_2 to afford the 1-arylurazole (compound **1** in Table 1) required 9 h at room temperature (91% yield), reaction with 1,3-dimethoxybenzene required upwards of 4 days for completion. No reaction was observed at all with less electron-rich aromatic compounds, such as 3-methylanisole (even after a month), anisole, or mesitylene.

Trifluoroacetic acid has been used in the past to catalyze reactions of TADs with carbonyl compounds.[13] We surmised that TFA might serve as an effective catalyst for the electrophilic addition of TADs to substituted benzenes as well. To test this theory, 1 equiv of trifluoroacetic acid was added to a solution of MeTAD and 1,3,5-trimethoxybenzene. A 93% yield of urazole **1** was formed within 10 s (Table 1, entry 1). This was a substantial rate enhancement relative to the corresponding room temperature reaction. Similarly, the addition of an equivalent of TFA to the reaction of MeTAD and 1,3-dimethoxybenzene resulted in a much faster reaction (5 min) to afford urazole **2** relative to the uncatalyzed reaction (see entry 4). The addition of TFA also effectively catalyzed reactions between MeTAD and otherwise thermally unreactive aromatics such as 3-methylanisole (Table 1, entry 5). The TFA-catalyzed reactions of MeTAD with several other substituted benzenes are collected in Table 1. Generally, good-to-high yields of 1-arylurazoles were obtained in reasonable reaction times.

Three general trends in reactivity were observed. First, despite the potential for formation of regioisomers, generally the formation of a single regioisomer corresponding to substitution of the



Scheme 1. General reaction of TAD with substituted benzenes to form 1-arylurazoles.

* Tel.: +1 706 290 2661; fax: +1 706 238 7855.
E-mail address: gbreton@berry.edu

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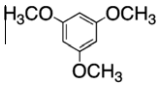
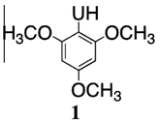
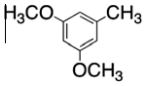
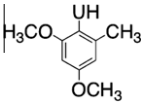
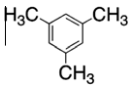
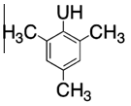
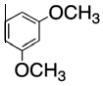
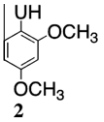
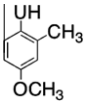
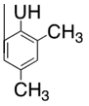
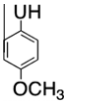
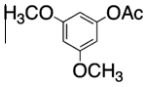
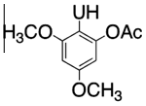
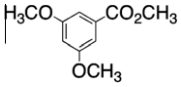
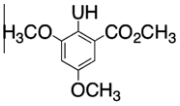
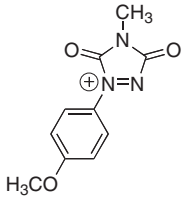
Table 1
TFA-catalyzed reactions of MeTAD with substituted aromatics[a,b]

Entry	Substrate	Conditions	Product	Yield (%)
1		1 equiv, CH_2Cl_2, rt, <1 min	 **1**	93
2		1 equiv, CH_2Cl_2, rt, <1 min		98
3		2 equiv, $CHCl_3$, 62 °C, 7 h		99
4		1 equiv, CH_2Cl_2, rt, 5 min	 **2**	79
5		2 equiv, $CHCl_3$, 62 °C, 10 min		99
6		2 equiv, $CHCl_3$, 62 °C, 24 h		54
7		2 equiv, neat anisole, rt, 2 h		53[c]
8		1 equiv, CH_2Cl_2, rt, 1 h		96
9		2 equiv, CH_2Cl_2, rt, 3 h		92

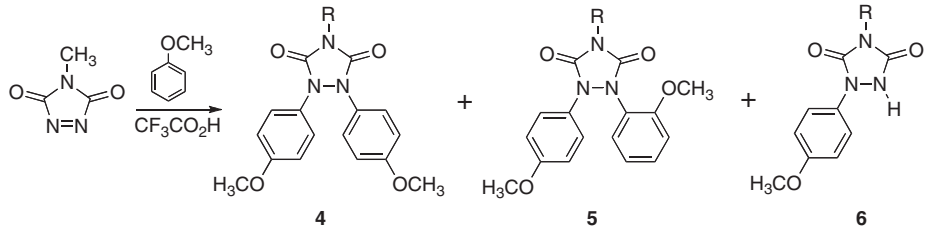
[a] All reactions were conducted according to a standard procedure unless otherwise specified: MeTAD (1 mmol) was added to a stirring solution of the substituted benzene (1.5 mmol) in 10 mL of solvent. The acid catalyst (equivalents provided in the Table) was added via syringe. If the reaction required heating, the solution was heated at reflux with a drying tube attached to the reflux condenser. Upon completion of the reaction, the solvent was removed via rotary evaporation. The resulting reaction mixture was subjected to column chromatography on SiO_2 using ethyl acetate as eluent. Characterization information for all new compounds is provided in Supplementary data.
[b] UH = *N*-4-methylurazole with N-1 attached to the aromatic ring and N-2 attached to an H.
[c] A 19% yield of compounds **4** and **5** (in a 60:40 ratio) was also isolated.

urazole ring at the position *para* to the strongest electron-donating substituent was observed (see, for example, entries 5 and 9). Second, less electron-rich aromatic compounds required the addition of 2 equiv of TFA and heating to reflux (in chloroform) to effect reaction (entries 3 and 5). The limit of reactivity appeared to be *m*-xylene where only a 45% yield of adduct was realized after 24 h. Reaction failed with benzene (used as solvent, 2 equiv of TFA, 80 °C), even upon prolonged heating (36 h). Finally, reaction was only feasible with benzenes upon which substitution *para* to an electron-donating substituent was possible. Thus, while 1,3-dimethoxybenzene afforded a high yield of 1-arylurazole **2**, 1,4-dimethoxybenzene failed to yield any urazole products at all. Similarly, whereas reaction with mesitylene was successful, reaction with durene (1,2,4,5-tetramethylbenzene) led to complex reaction mixtures with only trace amounts of the expected 1-arylurazole being detected.

Interestingly, attempted reaction with anisole under standard reaction conditions (1.5 equiv substituted benzene, 2 equiv TFA) failed to yield the expected 1-arylurazole product. Instead, an isomeric mixture of 1,2-diaryl substituted urazoles **4** and **5** (Scheme 2) was isolated in 62% yield (60:40 ratio, respectively). However, when the reaction was conducted in *neat* anisole, a 53% yield of 1-arylurazole **6** was afforded, and only a 19% yield of the disubstituted urazoles was isolated. To explain the formation of 1,2-diaryl substituted compounds, we propose that the initially formed 1-arylurazole **6** is capable of further oxidation, presumably to an electrophilic species such as **7**. Intermediate **7** may then undergo further reaction with anisole. An intermediate similar to **7** has been proposed earlier.[6] Interestingly, we did not observe the formation of disubstituted urazoles in any of the other reactions. The scope and mechanism of this interesting reaction is under current investigation.



7



Scheme 2. TFA-catalyzed reaction of MeTAD with anisole.

In conclusion, TFA-catalyzed reactions of MeTAD with substituted aromatics afford good-to-excellent yields of 1-arylurazoles under reasonable reaction conditions. The scope of the reaction is limited to fairly electron-rich benzenes with an available reaction site *para* to an electron-donor group. The reaction is tolerant of commonly encountered functionalities, such as alkyl, carbomethoxy, and acetoxy groups. The mechanism of formation of disubstituted urazoles **4** and **5** remains to be further investigated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.024.

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