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Synthesis of 2-amino-5-substituted-1,3,4-oxadiazoles using 1,3-dibromo-5,5-dimethylhydantoin as oxidant

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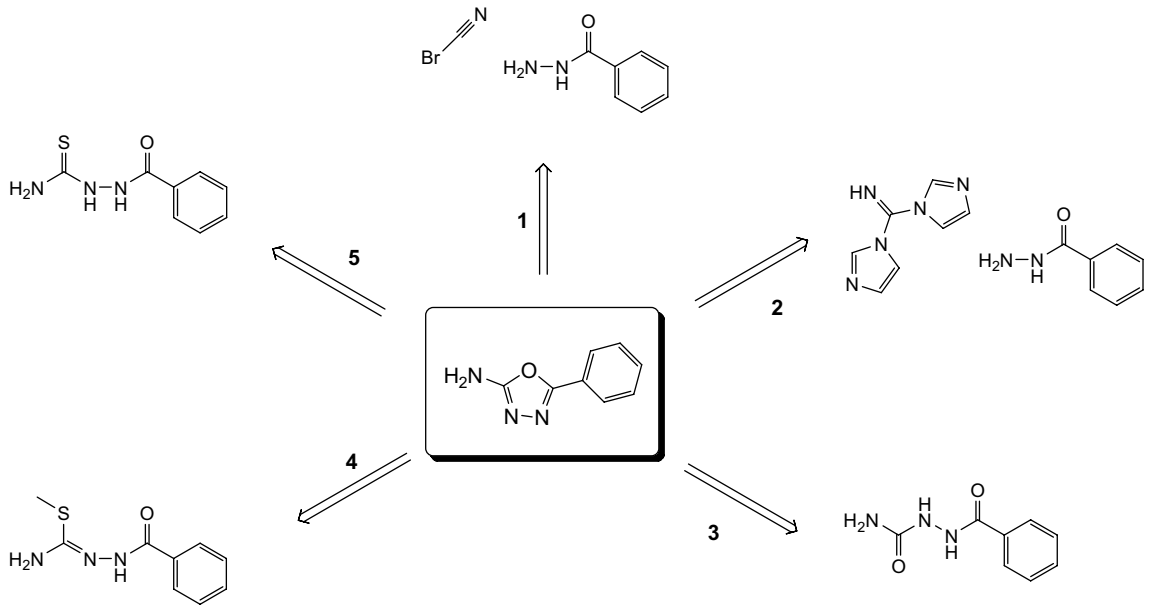
Abstract—A scalable synthesis of 5-substituted-2-amino-1,3,4-oxadiazoles via oxidation of a thiosemicarbazide precursor is described. The thiosemicarbazide intermediates are easily accessed from the corresponding acid chlorides. Oxidative cyclization using 1,3-dibromo-5,5-dimethylhydantoin as the primary oxidant, in the presence of potassium iodide, gives a variety of oxadiazoles in good yields. This methodology utilizes a commercially inexpensive and easily handled oxidant.

Molecules containing a 1,3,4-oxadiazole core have been shown to have a broad range of important biological activities including antibacterial,[1] antimicrobial,[2] hypotensive,[3] insecticidal,[4] herbicidal, and antifungal[5] properties. As part of an ongoing drug development program, we required an efficient and scalable method to prepare 2-amino-oxadiazole containing molecules.

Some of the methodologies reported in the literature to prepare this type of compounds are summarized in Scheme 1. Approaches 1 and 2 involve the formation



Scheme 1. Retrosynthetic approaches to amino-oxadiazoles.

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of the desired heterocycle via a hydrazide intermediate.[6] The preparation of these intermediates requires the use of hazardous hydrazine, which made these approaches undesirable for large scale synthesis. The dehydration of diacylhydrazides[7] (approach 3) has also been used to prepare the desired heterocycle, although it requires harsh conditions. Finally, acylthiosemicarbazide intermediates have been used in different ways to generate 2-amino-1,3,4-oxadiazoles. Sulfur methylation of an acylthiosemicarbazide induces cyclization (approach 4).[8] However, this strategy involves the use of toxic methylating reagents and generates volatile thiols as a byproduct of the reaction. Acylthiosemicarbazides can be cyclized to the corresponding oxadiazoles via carbodiimide mediated cyclizations[9] but there are issues of either cost or rejection of urea byproducts associated with this approach. Alternatively, acylthiosemicarbazides can be cyclized by oxidation with iodine[10] at elevated temperatures (approach 5).

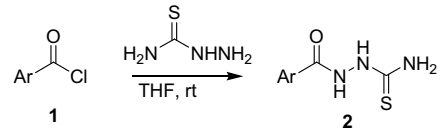
From both a safety and an economical standpoint, we were interested in the oxidative cyclization of acylthiosemicarbazides to prepare the desired 2-amino-1,3,4-oxadiazole. However, there are some liabilities associated with handling iodine on large scale including its high cost, the stability of iodine solutions, and its corrosive and lachrymatory properties. Thus, we set out to find an alternative oxidant that was economical and could be safely handled in large scale. Herein we report the use of 1,3-dibromo-5,5-dimethylhydantoin as the primary oxidant, in the presence of potassium iodide, for the oxidative cyclization of acylthiosemicarbazides.

In addition to exploring various oxidative cyclization methods, an expedient synthesis of the acylthiosemicarbazide intermediate would be desirable as well. Traditional methods for preparing this intermediate include reacting acylhydrazines with isothiocyanates or potassium thiocyanates.[11] We found that treating the appropriate acid chloride with thiosemicarbazide in THF was a straightforward method to prepare the desired acylthiosemicarbazide intermediate in good to excellent yields (Table 1).[12]

With the acylthiosemicarbazide intermediate in hand, a number of oxidants were examined to promote the cyclization (Table 2). Oxidants such as mCPBA, H_2O_2 and bleach (entries 1–3) gave some product but in low yields. Addition of catalytic amounts of iodine, TEMPO, or KI with bleach as terminal oxidant did not improve the yields in any appreciable amounts (entries 4–6). *N*-Bromosuccinimide gave moderate yields that could probably be improved with optimization but the succinimide byproduct was difficult to remove completely in the downstream chemistry.

1,3-Dibromo-5,5-dimethylhydantoin (entry 8) also proved to be a competent oxidant in this reaction. Unlike NBS however, the resulting dimethylhydantoin byproduct is highly water soluble and can be easily rejected during aqueous work-up. Furthermore, since both bromine atoms on the hydantoin are utilized for the oxidation, a substoichiometric amount of hydantoin is enough to drive the reaction to completion. The addition of catalytic amounts of KI to the reaction, further boosted the yields obtained.

Table 1. Synthesis of thiosemicarbazides[13]



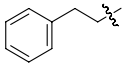
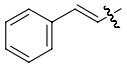
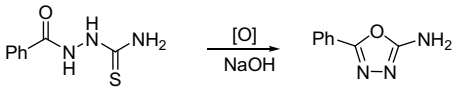
2	Ar	Yield of **2** (%)
a	Ph	88
b	4-Cl–Ph	92
c	4-OMe–Ph	92
d		68
e		85
f		72

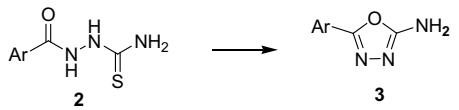
Table 2. Oxidant screen



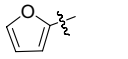
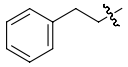
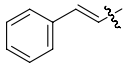
Entry	Oxidant	Additive	Assay yield (%)
1	mCPBA	None	4
2	H_2O_2	None	4
3	Bleach	None	23
4	Bleach	Iodine	27
5	Bleach	TEMPO	24
6	Bleach	KI	18
7	NBS	None	59
8	Hydantoin	None	63
9	Hydantoin	KI	75

After optimization of the reaction conditions, we found 0.75 equiv of 1,3-dibromo-5,5-dimethylhydantoin in the presence of 0.3 equiv of potassium iodide, with NaOH as base and isopropyl alcohol/acetonitrile as solvent, effectively gives the desired 5-substituted-2-amino-oxadiazole in high yield and purity. Presumably, iodine is generated in situ as indicated by the brown color formed during the course of addition of 1,3-dibromo-5,5-dimethylhydantoin solution to the reaction mixture containing substrate and potassium iodide. Alcoholic solvents work well for this reaction, although some decomposition of the acylthiosemicarbazide by transesterification was observed when ethanol or methanol were used. This side reaction was completely suppressed when isopropyl alcohol was used. Organic bases such as triethylamine or DBU may be used in the reaction. Using the optimized conditions, a number of 2-aminoxadiazoles were prepared in good yields as shown in Table 3. Various aryl substrates are tolerated as well as alkyl, alkenyl, and heterocyclic compounds. Although 1,3-dibromo-5,5-dimethylhydantoin has been used as a brominating reagent,[14] no brominated side products were found under these conditions.

Table 3. Synthesis of amino-oxadiazoles[15]



2 **3**

3	Ar	Yield of 3[a] (%)
a	Ph	75
b	4-Cl–Ph	88
c	4-OMe–Ph	97
d		83
e		53[b]
f		74

Conditions: 5 N NaOH, KI, H_2O, *i*PrOH, 1,3-dibromo-5,5-dimethylhydantoin, ACN 5 °C.

[a] Assay yields reported as determined by HPLC analysis.

[b] 15% of starting material was recovered.

A yellow solid was obtained as a byproduct of the reactions and determined to be elemental sulfur by analysis. The formation of this byproduct seems to indicate that under basic conditions and in the presence of an oxidant, the reaction proceeds via formation of a dithiane species. This would then be followed by cyclization to form the oxadiazole ring with simultaneous extrusion of sulfur.

In summary, we presented an expedient route to various 2-amino-5-substituted-1,3,4-oxadiazoles. The acylthiosemicarbazide intermediate is accessed easily by reacting an acid chloride with thiosemicarbazide. Cyclization via desulfurization using 1,3-dibromo-5,5-dimethylhydantoin as the primary oxidant, in the presence of potassium iodide, gives a variety of oxadiazoles in good yields. The main advantage to this approach is that the reagents used are commercially inexpensive and safe to handle. This methodology offers a safe alternative to current oxidative cyclization methodologies, and is especially applicable for large scale synthesis where the use of other oxidants may be prohibitive.

References and notes

1. (a) Ates, O.; Kocabalkanli, A.; Sanis, G. O.; Ekini, A. C.; Vidin, A. *Drug Res.* **1997**, *47*, 1134–1138; (b) Dabhi, T. P.; Shah, V. H.; Parikh, A. R. *Indian J. Pharm. Sci.* **1992**, *54*, 98–100; (c) Hui, X. P.; Zhang, L. M.; Zhang, Z. Y.; Wang, Q.; Wang, F. *Indian J. Chem. Sect. B. Org. Chem. Incl. Med. Chem.* **1999**, *38*, 1066–1069.
2. (a) Holla, B. S.; Gonsalves, R.; Shenoy, S. *Eur. J. Med. Chem.* **2000**, *35*, 267–271; (b) Cesur, N.; Birteksoz, S.; Otuk, G. *Acta Pharm. Turcica* **2002**, *44*, 23–41; (c) Laddi, U. V.; Desai, S. R.; Bennur, R. S.; Bennur, S. C. *Indian J. Heterocycl. Chem.* **2002**, *11*, 319–322.
3. Tyagi, M.; Kumar, A. *Oriental J. Chem.* **2002**, *18*, 125–130.
4. Zheng, X.; Li, Z.; Wang, Y.; Chen, W.; Huang, Q.; Liu, C.; Song, G. *J. Fluorine Chem.* **2003**, *123*, 163–169.
5. Zou, X.-J.; Lai, L.-H.; Jin, G.-Y.; Zhang, Z.-X. *J. Agric. Food Chem.* **2002**, *50*, 3757–3760.
6. For example: (a) Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090–1099; (b) Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *J. Heterocycl. Chem.* **2003**, *40*, 191–193.
7. For example: (a) Fulop, F.; Semega, E.; Dombi, G.; Bernath, G. *J. Heterocycl. Chem.* **1990**, *27*, 951–955; (b) Gehlen, H.; Mockel, K. *Justus Liebigs Ann. Chem.* **1965**, *685*, 176–180; (c) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112–3120.
8. Fulop, F.; Semega, E.; Dombi, G.; Bernath, G. *J. Heterocycl. Chem.* **1990**, *27*, 951–955.
9. For example: (a) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2001**, *42*, 2583–2586; (b) Baxendale, I. R.; Ley, S. V.; Martinelli, M. *Tetrahedron* **2005**, *61*, 5323–5349; (c) Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett.* **2004**, *45*, 3257–3260.
10. For example: (a) Zhang, R.; Qian, X.; Li, Z. *J. Fluorine Chem.* **1999**, *93*, 39–43; (b) Gani, R. S.; Pujar, S. R.; Gadaginamath, G. S. *Indian J. Heterocycl. Chem.* **2002**, *12*, 25–28.
11. For example: (a) Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett.* **2004**, *45*, 3257–3260; (b) Zhang, R.; Qian, X.; Li, Z. *J. Fluorine Chem.* **1999**, *93*, 39–43.
12. Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090–1099.
13. *Preparation of benzoyl thiosemicarbazide* (**2a**). Benzoyl chloride **1a** (5.0 g, 35.6 mmol) was dissolved in THF (75 mL) and the solution was cooled to 15 °C. Thiosemicarbazide (7.1 g, 77.9 mol) was then added portionwise and the reaction mixture was aged at room temperature for several hours. After the reaction was complete, the solution was quenched with aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (100 mL). The organic layer was then washed with aqueous $NaHCO_3$ (50 mL), then brine (50 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting solid was slurried in H_2O (50 mL) at room temperature, filtered and dried to give **2a** (6.08 g, 88% isolated yield).
14. For example: (a) Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1997**, *38*, 4415–4416; (b) Ishizumi, K.; Ohashi, N.; Tanno, N. *J. Org. Chem.* **1987**, *52*, 4477–4485.
15. *Preparation of 2-amino-5-phenyl-1,3,4-oxadiazole* **(3a)**. Benzoyl thiosemicarbazide **2a** (1.0 g, 5.12 mmol) was taken up in *i*PrOH (8 mL) to which was added a solution of KI (0.255 g, 1.54 mmol) in H_2O (2 mL) at room temperature. The solution was then cooled to 5 °C and 5 N NaOH (1.54 mL, 7.7 mmol) was added to give a clear homogeneous solution. A solution of 1,3-dibromo-5,5-dimethylhydantoin (1.1 g, 3.85 mmol) in acetonitrile (10 mL) was then added to the reaction mixture over 1 h while maintaining the temperature under 10 °C. After the addition, the mixture was aged for 1 h at this temperature and the reaction was quenched with aq $NaHSO_3$ (0.25 mL). EtOAc (25 mL) was then added to the slurry, the solids filtered and washed with EtOAc (10 mL). The filtrate was washed twice with $NaHCO_3$ (2×15 mL) and once with brine (15 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated. The resulting solid was slurried in H_2O (10 mL), filtered and slurry washed with EtOAc (2×2 mL) to give **3a** (507 mg, 62% isolated yield).