Tetrahedron Letters 52 (2011) 5750–5751

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Cyclization of protected *N*-acylhydroxyguanidine to 3-amino-1,2,4-oxadiazole

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ARTICLE INFO

Article history:
Received 1 August 2011
Revised 12 August 2011
Accepted 13 August 2011
Available online 26 August 2011

Keywords:
N-Acylhydroxyguanidine
3-Amino-1,2,4-oxadiazole
Acylthiourea
Cyclization
Heterocycle

ABSTRACT

The acid mediated cyclization of a protected *N*-acylhydroxyguanidine into the corresponding 3-amino-1,2,4-oxadiazole and confirmation of its structure by single crystal X-ray crystallography is reported herein. The yield of the cyclization is comparable to literature reports utilizing alternative procedures. Importantly, these new conditions provide complementary chemoselectivity to current synthetic procedures which may be useful for the synthesis of 3-amino-1,2,4-oxadiazoles in general.

Substituted 1,2,4-oxadiazole heterocycles (generic structure with IUPAC numbering shown in Fig. 1) are of interest to medicinal and organic chemists as they are present in a number of biologically active compounds.[1,2]

For example, a 3-amino-1,2,4-oxadiazole ring was recently identified for the first time in a natural product, phidianidine A (Fig. 1), isolated from a marine organism.[1] Further, 1,2,4-oxadiazoles are used in medicinal chemistry programs as prodrugs and bioiososteres of amides or esters.[2–4] Tropane derivative RTI-126 is reported to have five times greater biological activity than that of cocaine.[2] The synthesis and biological activity of 1,2,4-oxadiazole compounds have been recently reviewed.[4] There are numerous syntheses of 3-amino-1,2,4-diazoles reported in the literature but none of the reported methods are truly general.[4,5] The syntheses typically utilize high temperatures (~10 h at reflux) in acid or base to cyclize hydroxylamine with an acylthiourea. Here we report a room temperature, acid-catalyzed cyclization reaction to yield 3-amino-1,2,4-oxadiazoles. The low temperature utilized may allow for the synthesis of novel 3-amino-1,2,4-diazoles that are otherwise not accessible using hitherto reported methods.

Our synthesis commenced with the commercially available acid chloride **1** (Scheme 1). The acylthioisocyanate of **1** was prepared in situ using a literature procedure[6] and converted to acylthiourea **2** by reaction with 1-naphthylamine. Intermediate **2** was treated with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, EDCI, and triethylamine to afford **3** in excellent yield.[7] Treatment of **3** with acid did not provide the *N*-hydroxyguanidine as expected.[7] The only isolated product from this reaction was determined by single crystal X-ray analysis to be 3-amino-1,2,4-oxadiazole **4** (Fig. 2).[8] The mechanism of this cyclization reaction can be rationalized as depicted in Scheme 2. Following literature precedent for acid-mediated cleavage of tetrahydropyranyloxy ether-protected guanidines[7], we treated intermediate **3** with trifluoroacetic acid. Protonation of the tetrahydro-2*H*-pyran-2-yl (THP) hydroxyl group and tautomerization of the guanidine moiety could lead to **5**, with subsequent cleavage of the THP group and protonation of the carbonyl oxygen atom leading to **6**. Nucleophilic addition of the *N*-hydroxyguanidine hydroxyl group of **6** onto the benzoyl moiety (leading to **7**), with subsequent elimination of H_2O and deprotonation, could lead to 3-amino-1,2,4-oxadiazole **4**.

The synthesis of 3-amino-1,2,4-oxadiazoles that we have developed proceeds in three steps with an overall yield of 30% (unoptimized), compared favorably with the reported values from alternate

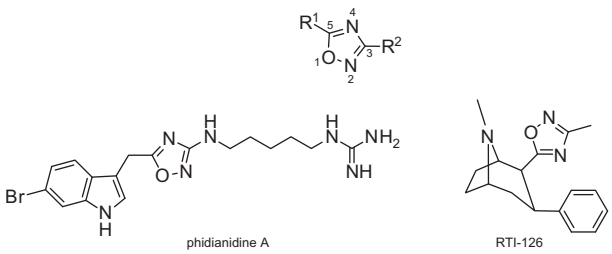

Figure 1. Examples of a 1,2,4-oxadiazole-containing natural product (phidianidine A) and biologically active compound (RTI-126).

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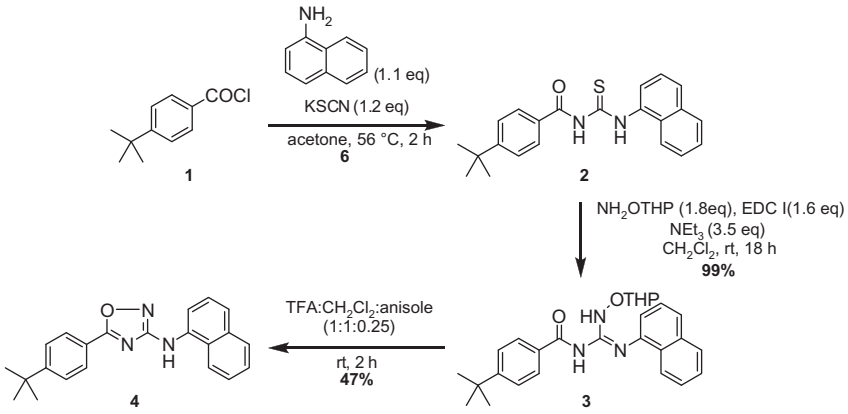
doi:10.1016/j.tetlet.2011.08.074



Scheme 1. Synthesis of 3-amino-1,2,4-oxadiazole **4** (THP = tetrahydro-2*H*-pyran-2-yl).

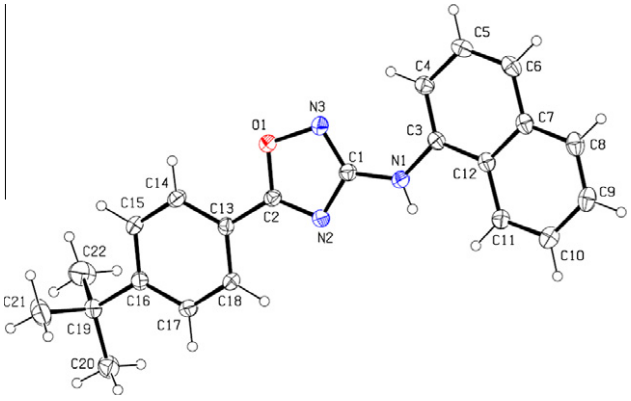
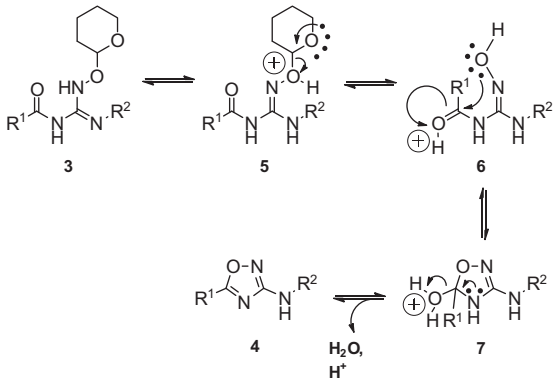


Figure 2. ORTEP depiction of the structure of 3-amino-1,2,4-oxadiazole **4**, as determined by single crystal X-ray analysis (spheroids depict nitrogen (blue), oxygen (red) or carbon (white); small circles depict hydrogen).



Scheme 2. Proposed mechanism for acid catalyzed cyclization (R^1 = 4-*tert*-butylphenyl; R^2 = 1-naphthyl).

methods. However, the lower reaction temperature identified here is a clear advantage for this method over previously reported methods and may prove useful for the synthesis of 3-amino-1,2,4-oxadiazoles containing sensitive functional groups.

Acknowledgment

We thank Dr. Alan J. Lough, Director of X-ray Facility, Department of Chemistry, University of Toronto, for obtaining the X-ray crystal structure data and generating the ORTEP depiction of compound **4**.

References and notes

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8. Synthesis of 5-(4-(*tert*-butyl)phenyl)-*N*-(naphthalen-1-yl)-1,2,4-oxadiazol-3-amine (**4**): (*Z*)-4-(*tert*-butyl)-*N*-(*N*′-(naphthalen-1-yl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)carbamimidoyl)benzamide (Intermediate **3**; 0.44 g, 0.98 mmol) was stirred at room temperature (rt) in a mixture of dichloromethane (5 mL) and anisole (2.5 mL). Trifluoroacetic acid (5 mL) was added. The mixture was stirred for ~2 h at rt and was then stored for 16 h at −20 °C. The mixture was concentrated by rotoevaporation and high vacuum to yield a crude brown oil that was subjected to ISCO semi-automated Flash Chromatography on silica gel (40 g), eluting with a gradient of 0→20% EtOAc in hexanes. The resulting white solid (159 mg) was stirred in 3 mL of hot hexanes, with full solution provided by the addition of minimal dichloromethane. The mixture was concentrated to ½ volume and allowed to stand at rt overnight. Crystals were collected by vacuum filtration, washed with cold hexanes and dried, yielding 79 mg of white needles. *Compound* **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13(d, 1H), 8.09 (d, 2H), 8.01 (d, 1H), 7.92 (d, 1H), 7.64–7.54 (m, 6H), 7.29 (s, 1H), 1.40 (s, 9H); chemical purity, 99% (AUC at 254 nm); LCMS: *m*/*z* 343.9 ($M+H^+$); mp: 118–119 °C; X-ray crystallography: A clear needle-like crystal of 0.65 × 0.14 × 0.08 mm^3 was used for data collection. X-ray diffraction was measured using radiation with a wavelength of 0.71073 Å at 150(1) K. The crystal showed a monoclinic crystal system, space group *P*21/c. Crystal data are: $Z = 4$, $a = 11.4037(3)$ Å, $b = 20.0328(12)$ Å, $c = 7.9932(6)$ Å, $\beta = 101.299(3)°$, $V = 1790.64(18)$ Å^3, density (calcd) = 1.274 mg/m^3, absorption coefficient 0.080 mm^{-1}.