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Large-Scale Preparation of 3-Methyl-4H-[1,2,4]oxadiazol-5-one, Potassium or Sodium Salt

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Abstract:

The development of a safe and practical process for the potassium and sodium salts of 3-Methyl-4H-[1,2,4]oxadiazol-5-one 1A and 1B is described. The focus of the report is how the scale-up issues of the original procedure are overcome, in particular, the thermal hazards of the starting material, hydroxylamine, and the intermediate, acetamidoxime 4. The final process was demonstrated multiple times on a 600-L scale with consistent yields (70%) and purities (95%).

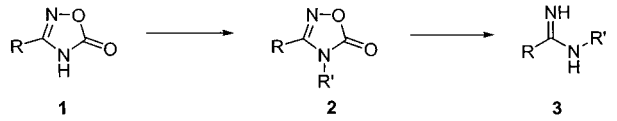
Introduction

Oxadiazolones **1**, **2** are versatile synthetic intermediates that serve as precursors and protecting groups for amidines **3**, an important class of biologic functionality.[1] The conversion to the parent amidines is readily achieved by mild reductive methods such as Pd/H_2 or Zn/AcOH (Scheme 1). During the course of a recent project a safe and operationally simple procedure to prepare multikilogram lots of the potassium salt of 3-Methyl-4*H*-[1,2,4]oxadiazol-5-one (**1A**) was needed (Scheme 2). Compound **1** has been converted to amidines by methods developed by Moormann et al.[2]

Discussion

The starting point for our scale-up work was a procedure based on the synthesis published by Harsányi et al.[3] This two-step procedure (Scheme 2) describes first the liberation of hydroxylamine free base from the hydrochloride using sodium ethylate in ethanol and then filtration to remove the resulting sodium chloride, followed by heating the filtrate at reflux with 1 equiv of acetonitrile. The acetamidoxime **4** was isolated as a solid in yields of 40−50% by concentrating the solution to dryness. The second step of the procedure involved treatment of a suspension of the acetamidoxime in diethyl carbonate with solid potassium *tert*-butoxide. This concentrated reaction mixture was troublesome as the reaction was very exothermic and heterogeneous. In fact, stirring became very difficult upon formation of large lumps. The product, potassium 3-methyl-4H-[1,2,4]oxadiazol-5-one **1A**, could nevertheless be isolated in high yield and purity by filtration, up to 50-g scale in the laboratory.

Scheme 1. **Oxadiazolones as precursors for amidines**



Scheme 2. **Original procedure for the synthesis of 1A**

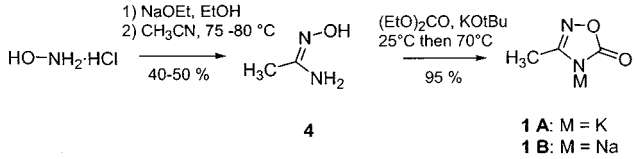


Table 1. **Thermokinetic data**

cmpd	*T* onset (°C) (exotherm [J/g])	melting point (°C) (heat of fusion [J/g])
acetamidoxime **4**	140 (−1253)	130 (202)
oxadiazolone-K **1A**	270 (−782)	264 (158)
oxadiazolone-Na **1B**	307 (−750)	278 (128)

However, the scale-up issues described above led us to develop an alternative procedure. Further investigations included thermokinetic analysis by DSC of the intermediate **4** and the final products **1A** and **1B** (Table 1).

While the final compounds **1A** and **1B** are relatively stable with onset temperatures well above operating temperatures, the intermediate **4** showed a prohibitively high exotherm with an onset temperature of 140 °C.[4] These data suggested decreasing the reaction temperature from 75 to 80 °C to below 40 °C and not to concentrate the solution for the isolation of **4**, but rather to telescope it with the next step. In addition it is well established that handling of hydroxylamine free base can be a dangerous enterprise[5] at elevated temperatures and in the presence of metal ions.

First Campaign Procedure. With these scale-up issues in mind, the following procedure for the first production campaign was designed. The temperature during liberation of hydroxylamine free base was decreased to 0−5 °C to minimize decomposition of hydroxylamine.[5,6] Filtration of

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(1) Bolton, R. E.; Coote, S. J.; Finch, H.; Lowdon, A.; Pegg, N.; Vinader, M. V. *Tetrahedron Lett.* **1995**, *36*, 4471.

(2) Moormann, A. E.; Wang, J. L.; Palmquist, K. E.; Promo, M. A.; Snyder, J. S.; Scholten, J. A.; Leschinsky, K. L.; Sikorski, J. A.; Webber, R. K. 3-Methyl-4H-[1,2,4]-oxadiazol-5-one: A Synthon and Protecting Group for the Methyl Amidine. Publication in preparation.

(3) Takács, K.; Harsányi, K. *Chem. Ber.* **1970**, *103*, 2330; Mindl, J.; Kavalek, J.; Strakova, H.; Sterba, V. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1641.

(4) A commonly accepted rule in the industry recommends an operation temperature of at least 100 °C below the observed onset temperature of unacceptably high exotherms.

(5) A very good collection of safety data on hydroxylamine free base is found on the BASF Website, http://www.basf.dk/en/produkte/chemikalien/anorganika/anorg_spezial/hydroxyl_fb/hafb_sucess.htm.

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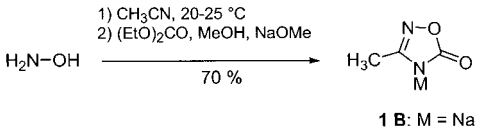
sodium chloride was postponed to a later stage of the process, when all hydroxylamine was consumed. The reaction temperature for the next step was lowered from reflux to 20 °C to avoid decomposition of hydroxylamine and to stay well below the onset temperature of decomposition of **4**. To compensate for the lower conversion rates, acetonitrile was added in excess rather than just in stoichiometric amounts.[3] This change also improved safety, as it decreased the likelihood of hydroxylamine decomposition.

Due to the thermal potential of **4**, telescoping was preferred over isolation. However, dark-colored byproducts were observed upon addition of diethyl carbonate and potassium *tert*-butylate, presumably due to the presence of acetonitrile. Weaker bases, such as potassium carbonate, did not initiate the ring-closing reaction. Thus, a solvent exchange of acetonitrile to methanol/diethyl carbonate was carried out by adding diethyl carbonate, followed by continuous addition of methanol and removal of acetonitrile to maintain a constant volume, whereby a potential adiabatic temperature increase, caused by decomposition of **4**, would not reach the boiling point of the reaction mixture.[7] When the acetonitrile was reduced to levels of 10%, the base-induced cyclization step occurred without colored byproducts. Running the last step in methanol avoided the heterogeneous nature of the original procedure and also improved the temperature control of this exothermic reaction step. A final solvent exchange to 2-propanol furnished crystallized **1A** as high-quality material in yields of 60%.

Second Campaign Procedure. Further improvements to the process were straightforward and focused on increasing throughput. To this end the free-basing procedure of hydroxylamine salt was omitted and commercially available aqueous hydroxylamine free base (50 wt %) used instead. This change saved two unit operations, that is, the liberation of the free base in ethanol and the filtration step. It also increased conversion rate due to a higher concentration of acetonitrile. The water was removed after formation of **4** during the solvent-exchange process to diethyl carbonate and methanol. Potassium *tert*-butoxide, the base for the cyclization, was replaced by a solution of sodium methylate in methanol, which was less expensive and, because it was purchased as a solution, simplified handling. This procedure generated the product as the sodium salt **1B**, which showed similar safety characteristics, but behaved superiorly in the downstream chemistry, due to improved solubility (Scheme 3).

Scheme 3. **Developed process for the synthesis of 1B**



1 B: M = Na

Summary

A safe and practical process for the potassium and sodium salts of 3-Methyl-4H-[1,2,4]oxadiazol-5-one **1A** and **1B** has been developed. This process was demonstrated multiple times on a 600-L scale with consistent yields (70%) and purities (95%).

Experimental Section

To a 640-L glass-lined reactor, charged with acetonitrile (170 L), was added hydroxylamine (50% aq, 15 L, 240 mol) over 15 min at 20−25 °C. After the mixture stirred at 20−25 °C for 24 h, hydroxylamine was undetectable (TLC SiO_2, CH_2Cl_2, MeOH, NEt_3 70:30:1, 1% ninhydrin in EtOH, $R_f(NH_2OH) = 0.17$, $R_f(\mathbf{4}) = 0.24$). The reaction mixture was analysed by GC for the content of **4** to assess the amount of sodium methoxide necessary (typically 210 mol of **4** were formed). Diethyl carbonate (217 L) was added to the reaction mixture followed by distillation of 190 L of acetonitrile/water at 30 °C, at 90−110 mbar. Methanol (312 L) was added as the distillate was removed. At the end of the distillation process the reaction mixture was analysed by GC for acetonitrile (less than 10%). Sodium methoxide in methanol (5.4 M, 40 L, 216 mol) was added over a period of 30 min at 10−15 °C. After addition was complete, the reaction mixture was heated to 67−70 °C and stirred for 5 h (TLC see above). The reaction mixture was concentrated at 50−60 °C to a volume of 50−60 L at 100 mbar and diluted with 2-propanol (167 L). The suspension was heated to 67−70 °C, stirred at that temperature for 1 h, and cooled to 0−5 °C, and stirring continued for 12 h. The suspension was filtered or centrifuged and dried at 40 °C and 25 mbar to give **1B** (20.7 kg, 70%) as a white solid. The purity was determined by NMR (using hydroquinone as internal standard) to be 95%.

^{1}H NMR (400 MHz, DMSO): δ 1.85 ppm (s); ^{13}C NMR (100 MHz, DMSO): δ 13.00, 166.42, 173.91 ppm.

IR (ATR): ν = 1624, 1535, 1416, 1362, 1227, 1088, 1069, 1020, 951, 905, 824, 786 cm^{-1}.

Anal. Calcd for for $C_3H_3N_2NaO_2$ (122.06): C 29.52, H 2.48, N 23.0; Na 18.84; found: C 29.03, H 2.54, N 22.60; Na 18.60

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(6) As an additional safety precaution, water was filled in the feed vessels for a safety quench, in case of an unexpected thermal event during the liberation of hydroxylamine free base.

(7) Acetamidoxime **4** decomposes with a release in energy of 1253 J/g. A rough estimate using an average heat capacity of 2 J/g K for organic solvents with a minimum dilution of 1:12 calculated to an adiabatic temperature rise of 52 °C. After diethyl carbonate is added, **4** is rapidly consumed into an open-chain precursor of **1A**, which appears to be less reactive towards thermal decompostion. DSC analysis on reaction mixtures after the addition of diethyl carbonate never showed significant exotherms.