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# Synthesis of a stable triformylmethane synthon and its scalable application to 7-acylamino-3-formylquinoline syntheses

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ABSTRACT

Novel 2-iminiomethylvinamidinium trihalides were isolated as stable crystals and found to be useful triformylmethane synthons with non-deliquescent nature in air. They were easier to manufacture, handle, and store than the known 2-iminiomethylvinamidinium dichloride. By virtue of in situ aminal protection, a combination of the vinamidinium salt with a secondary amine achieved an efficient and scalable synthesis of 7-acylamino-3-formylquinoline, a versatile synthetic intermediate for potent anti-obesity drugs 7-acylamino-3-aminomethyl-8-methylquinolines.



## 1. Introduction

Obesity is a global pandemic.[1] Once considered a problem of high-income countries, obesity is now on the rise in low- and middle-income countries, particularly in urban settings. Existing strategies to combat obesity through lifestyle modification have had limited success and thus new classes of treatments, including pharmacotherapy, are being sought in an attempt to reverse the burden the disease has on all societies. Among the various anti-obesity drugs that have been developed, melanin-concentrating hormone receptor 1 (MCHR1) antagonists have been reported as especially promising agents and the non-peptide compounds **1** were found to be highly potent, orally bioavailable and centrally acting MCHR1 antagonists (Fig. 1).[2]

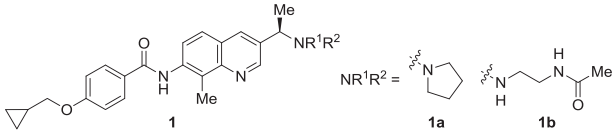
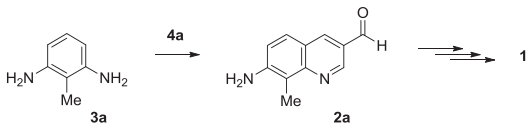
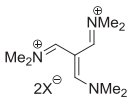



**Fig. 1.** MCHR1 antagonists **1**.

The potent drugs **1** are characterized by the core chemical structure of 7-acylamino-3-aminomethyl-8-methylquinoline. In their original synthesis, 7-amino-3-formyl-8-methylquinoline **2a** played a major role as a versatile intermediate leading to a series of MCHR1 antagonists (Scheme 1).[2c] The intermediate **2a** was originally synthesized by a quinoline annulation reaction of 2,6-diaminotoluene **3a** with the 2-iminiomethyl substituted vinamidinium (1,5-diazapentadienium) salt **4a** (structure in Fig. 2).




**Scheme 1.** Original synthesis of MCHR1 antagonists **1**.




**4a** (X=$BF_4$), **4b** (X=Cl), **4c** (X=$ClO_4$), **4d** (X=$PF_6$)

**Fig. 2.** Known 2-iminiomethylvinamidinium salts **4**.

Vinamidinium salts[3] are known to be applicable to a variety of aromatic ring annulations, such as substituted quinolines,[4] pyrimidines,[5–7] pyrroles,[8] isoxazoles,[9] pyridines,[10–13] benzenes,[14,15] and fused pyrimidines and pyridines,[16–18] and the

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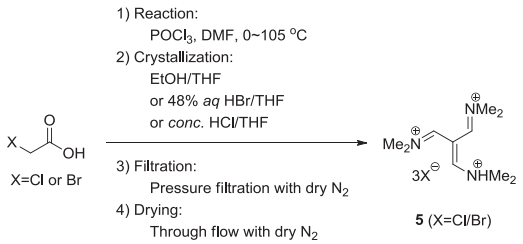
synthetic approach has attracted much attention in not only academia but also industry. As an industrial example, a vinamidinium salt has been used for a pyridine annulation step in the manufacturing process of Etoricoxib.[12] Among the various vinamidinium salts, 2-iminiomethyl substituted vinamidinium salts **4** have become the focus of attention since they can serve as a triformylmethane synthon.[9,19,20] As a synthetic reagent, however, **4** has the commonly noted issue of being hygroscopic. In particular, the Cl salt **4b** is deliquescent leading to decomposition[21] and it is difficult to handle it on large-scale. To overcome the hygroscopicity and deliquescent nature, the $ClO_4$ salt **4c** was developed and used as an alternative.[5,8] Since a safety assessment revealed that **4c** has high energy content and shock sensitivity,[22,23] the $BF_4$ salt **4a** has been introduced as an alternative, although it suffers the drawback of showing glass corrosion properties.[4,9] In recent years the non-hygroscopic $PF_6$ salt **4d** has been discovered and applied for various syntheses.[24] However, **4d** has the drawback of requiring a costly $PF_6$ anion source.

As part of a drug development program, we recently required access to a scalable and efficient synthesis of the 7-aminosubstituted 3-formylquinoline **2**. Although a variety of quinoline syntheses have been reported, to our knowledge, the only existing synthesis of **2** was the method depicted in Scheme 1.[2b,c,4] Our attention was focused on an application of this methodology, scouting for a novel 2-iminiomethylvinamidinium salt suitable for a large-scale production with the following characteristics: (1) stable in air, (2) non-glass-corrosive, and (3) inexpensive manufacture using common materials. We thought a vinamidinium salt of such nature would become a generally useful tool for aromatic ring annulations. Herein, we report a novel, stable 2-iminiomethylvinamidinium trihalide **5** and its application to an efficient quinoline annulation reaction to provide **2**, a versatile intermediate leading to MCHR1 antagonists **1**.




**Scheme 2.** Preparation of 2-iminiomethylvinamidinium trihalide **5**.

## 2. Results and discussion

### 2.1. Discovery of 2-iminiomethylvinamidinium trihalide

2-Iminiomethylvinamidium salts **4** have been synthesized via Vilsmeier–Haack type reaction using bromoacetic acid with DMF and phosphoryl chloride.[19] The reaction of phosphonoacetic acid,[5] trifluoropropanoic acid,[24] or malonic acid[15] with the Vilsmeier reagent also yielded **4**. Isolation of **4** has been achieved by crystallization from aqueous solution containing a counter anion such as $BF_4^-$, $ClO_4^-$, and $PF_6^-$.[5,15,19,24] For example, in the bromoacetic acid case (reagents ratio used; bromoacetic acid/DMF/phosphoryl chloride=1:15:3),[19] distillation of the remaining DMF and a successive addition of ice and aq $NaBF_4$ gave the desired crystals **4a**.

In our study, the commonly available bromoacetic acid was selected as the starting material and phosphoryl chloride and DMF were used for the in situ preparation of the Vilsmeier reagent (Scheme 2). An excess amount of DMF was used since DMF serves as not only the reagent but also reaction solvent (reagents ratio used; bromoacetic acid/DMF/phosphoryl chloride=1:6:4). We envisioned quenching of the reaction mixture with EtOH instead of water and crystallization of the halide salt by adding anti-solvent THF, which we anticipated would allow crystallization in a non-aqueous solution. In fact, a successive addition of EtOH and THF enabled crystallization directly from the reaction mixture and enabled us to avoid the tedious distillation of the high boiling point DMF. In order to prevent the crystals from absorbing moisture, the subsequent isolation process was carried out by pressure filtration and through-flow drying with dry $N_2$ (dew point: −80 °C).

Unexpectedly, the $^1$H NMR spectrum of the isolated crystals showed no peak at around 3.5 ppm in DMSO-$d_6$ due to water but a singlet peak at around 6.5 ppm, which indicated that the isolated vinamidinium salt was protonated by the acid side product (HCl/HBr). Thus, this procedure provided the unusual vinamidinium trihalide **5** (structure in Scheme 2) instead of the dichloride **4b**. An example of $^1$H NMR spectra of **5** (X=Cl) is shown in Fig. 3. To our knowledge, 2-iminiomethylvinamidinium salts have only been reported as the salts containing two molecules of counter anions such as **4a**–**d**. We believe this is the first report of a 2-iminiomethylvinamidinium salt, incorporating three molecules of counter anions.

Fortunately, **5** showed better physical properties and was non-deliquescent in air. Consequently, **5** can be easily handled as a synthetic reagent and has a long-shelf-life, only requiring to be kept in an air-tight container at room temperature. In fact, over 3

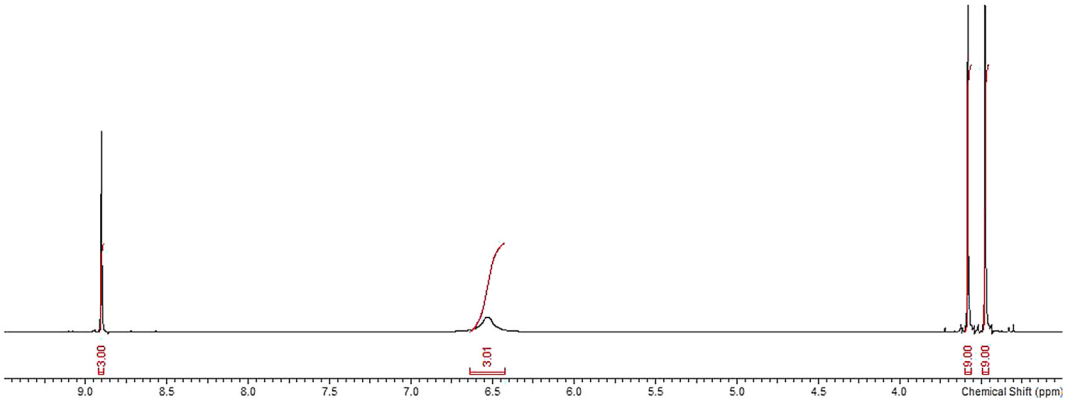



**Fig. 3.** $^1$H NMR spectra of **5** (X=Cl).