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Novel synthon for incorporating 1,3-dimethyl-imidazolium group into molecular architecture

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Abstract—The synthesized 1,3-dimethylated imidazolium-carbaldehydes serves as synthons for incorporating a permanently cationic imidazolium group into molecular framework. The utility of new synthon was demonstrated in a variety of reactions: Knoevenagel, Wittig, Schiff base formation, based-mediated electrophilic substitution, and oxidation, including synthesis of the natural product norzooanemonin.

Imidazole is an important functionality in biological systems and 5-imidazole-carbaldehydes, including their mono-N-methylated analogs are often used as building blocks in medicinal chemistry. Because methylation is the major histamine catabolic pathway in mammalian tissues, mono-N-methylated imidazole derivatives are commonly found in imidazole metabolites. Beside natural occurrence, other compounds bearing this group have been widely studied due to their anticancer,[1] antimalarial,[2] antibacterial,[3] antifungal,[4] and ocular antihypertensive[5] properties. In addition, several drugs and drug candidates (pilocarpine, tipifarnib) that incorporate *N*-methyl imidazoles have been developed. These findings have been facilitated by the commercial availability of suitable synthons such as 1-methyl-1*H*-imidazole-5-carbaldehyde for inclusion in SAR studies.

Although rare, di-N-methylated imidazolium occurs in natural compounds. Some examples include 1,3-dimethylhistidine, zooanemonin,[6] norzooanemonin, methyl ester of norzooanemonin, (+)-echinobetaine B,[7] Chrysophysarin A,[8] and the insect peptide extracted from *Heliothis virescens*[9] (Fig. 1). These compounds have some promising biological properties such as antiviral,[9] nematocidal, and antifouling[10] activities. Biologically, 1,3-dimethyl-imidazolium group is metabolically stable. For example, the methyl groups in 1,3-dimethylhistidine-1,3-$(C^{14}H_3)_2$ were not eliminated in a variety of animals studies.[11] Considering the potential usefulness of imidazolium-containing compounds, the availability of a suitable building block for its incorporation into diverse molecules would add an important functionality to a variety of compound libraries.

Unfortunately, 1,3-dimethyl-5-imidazolium-carbaldehyde suitable for facile incorporation of di-N-methylated imidazolium is unknown. With a few exceptions that include their use as protective agents against chemical weapons (soman),[12] non-natural basic amino acid-containing peptides,[13] and antibacterial compounds,[3] the literature is sparse on the use of dimethylated imidazolium-containing molecules in biological applications. There are number of synthetic[14] and enzymatic[15] methods available for the methylation of imidazoles. The most common chemical method utilizes MeI as the alkylating agent. Although the methylation of N-1 proceeds smoothly even at low temperature, alkylation of the tertiary N-3 requires prolonged heating at high temperature, for several days,[16] apparently due to the reduced nucleophilicity of the N-3 atom.[17]

In this Letter, we describe an effective method to prepare imidazoliums by using trimethyloxonium salts, also known as Meerwein salt,[18] which has been used previously to quaternize a variety of heterocyclic amines.[17,19] We also report solvent dependent tautomerism of the synthesized compounds and their ability to participate in different reactions.

Imidazole **3** is soluble in ethylacetate,[20] while the alkyloxonium salt has a low solubility. Because of this limited solubility, the reaction mixture is heterogeneous

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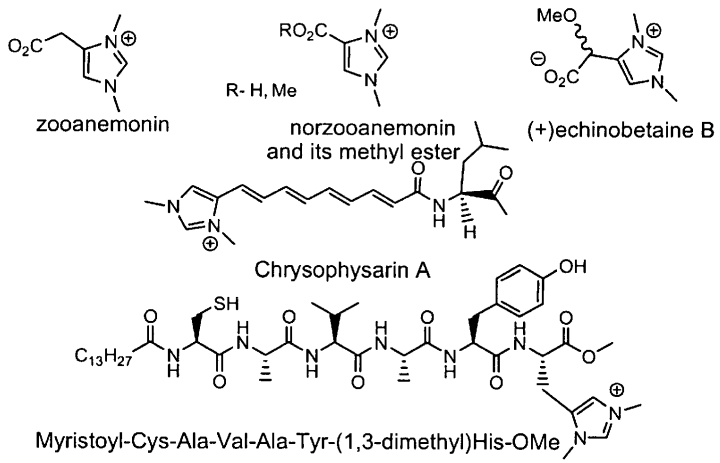
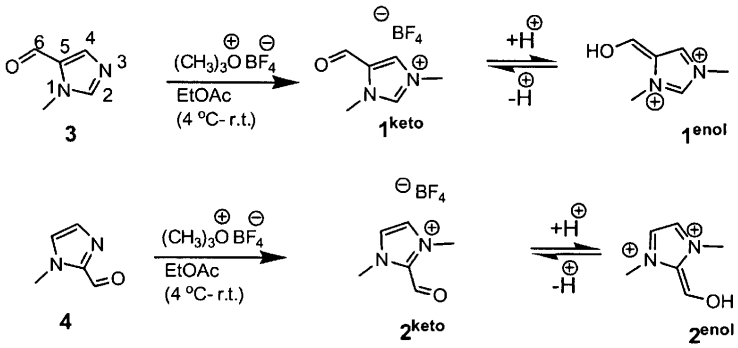


Figure 1. Naturally occurring 1,3 dimethyl 5-imidazoliums.

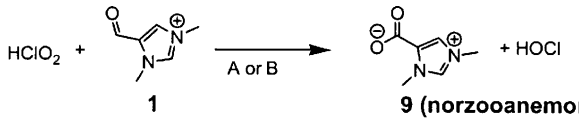


Scheme 1. Synthesis of 1,3-dimethyl-5-imidazolium-carbaldehyde and 1,3-dimethyl-2-imidazolium-carbaldehyde and their tautomerism. $\mathbf{1}^{keto} + \mathbf{1}^{enol}$, yield ~95%; $\mathbf{2}^{keto} + \mathbf{2}^{enol}$, yield ~91%.

and the alkylation occurs either at the surface of the suspended alkyloxonium salt or in the dilute solution phase.[17]

Upon alkylation, the insoluble 1,3-dimethyl-5-imidazolium-carbaldehyde **1** (Scheme 1) is precipitated from the reaction mixture as the tetrafluoroborate salt. Side-products were not detected, thereby eliminating the need for a further work-up. The reaction was fast, quantitative and only required mixing the reaction mixture and collecting the desired compound on a filter. In contrast, alkylation with MeI under the same conditions described above did not give the desired compound, leaving the starting material intact. To demonstrate the generality of the alkylation method, 1,3-dimethyl-2-imidazolium-carbaldehyde **2** was also prepared in the same manner (Scheme 2). Although **2** has been reported previously,[21] the literature description of its synthesis and usage is sketchy.[19,20]

Analyses of the ^{1}H NMR spectra showed that compounds **1** and **2** exhibit interesting solvent dependent tautomeric properties (Table 1). This is indicated by the disappearance of the signals corresponding to aldehyde protons (9.86 ppm for **1** and 9.93 ppm for **2**) and appearance of enol proton signals upfield (5.60 ppm for **1** and 6.05 ppm for **2**). In methanol, dimethylated imidazoliums **1** and **2** exist exclusively in the enol form, suggesting their stabilization by proton transfer while in aprotic DMSO the keto form is favored. The starting material mono-methylated 5-imidazole **3** does not show solvent dependent tautomeric properties, remaining exclusively in a keto-form. The mono-methylated 2-imidazole **4** demonstrates only some degree of tautomerism. In the solid form, **1** and **2** are in the keto form, as evidenced by the characteristic band of carbonyls at 1700 cm^{-1} in the IR spectra and in the absence of peaks corresponding to alcohols (see Supplementary data). Despite the structural similarities between **1** and **2**, the compounds have drastically different physical properties, such as melting points: **1** ~57 °C and **2** ~180 °C.



Scheme 2. Synthesis of norzooanemonin by the oxidation of dimethyl-imidazolium-carbaldehyde. Reagents and conditions: (A) $NaClO_2$, KH_2PO_4, water, DMSO, rt, 20 min; (B) resin-ClO_2, resin-H_2PO_4, water, DMSO, rt, 1 h, 89%.

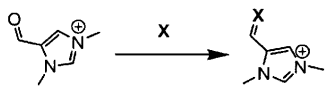
Table 1. Keto–enol tautomer composition in different solvents determined by ^{1}H NMR

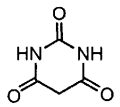
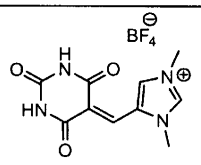
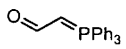
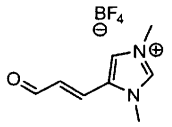
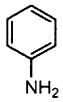
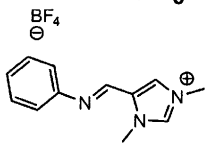
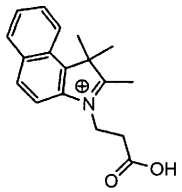
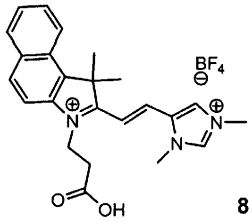
Compound	Solvent	δ^a (2-H)	δ^a (4-H)	δ^a (5-H)	δ^a (6-H)	Enol (%)	Keto (%)
1	DMSO-d_6	9.26	8.53	—	9.86	0	100
1	Methanol-d_4	8.75	7.54	—	5.60	100	0
2	DMSO-d_6	—	7.89	7.89	9.93	0	100
2	Methanol-d_4	—	7.48	7.48	6.05	100	0
3	DMSO-d_6	8.01	7.88	—	9.76	0	100
3	Methanol-d_4	7.91	7.84	—	9.76	0	100
4	DMSO-d_6	—	7.61	7.27	9.71	0	100
4	Methanol-d_4	—	7.41^{keto} 7.00^{enol}	7.24^{keto} 6.83^{enol}	9.72^{keto} 5.62^{enol}	28	72

[a] ppm, relative to TMS.

The versatility of **1** as a synthon was demonstrated by its utility in a variety of classical organic reactions, such as Knoevenagel condensation, Wittig reaction, Schiff base formation, and base-mediated electrophilic substitution (Table 2). Knoevenagel condensation was conducted in water at room temperature following a recently published procedure[22] by simply adding a stoichiometric amount of barbituric acid to an aqueous solution of **1**. After 4 h, the solid formed was filtered, washed with a small amount of cold water and dried. Solubility of the formed compound **5** in water resulted in a relatively low yield (54%). Higher yields could be obtained by recovering the portion of **1** in the filtrate. Wittig reaction was performed in DCM at room temperature. Although **1** is not soluble in non-polar solvents, its low melting point allowed us to generate a biphasic liquid solution in DCM by heating to 60 °C in a closed reaction vessel. After cooling the biphasic solution, (triphenylphosphoranylidene)acetaldehyde was added to the reaction mixture, which was vigorously stirred for 20 h. The precipitate was washed with DCM and methanol and dried. Spectroscopic studies (^{1}H NMR, DMSO-d_6) showed desired aldehyde **6** was obtained in a high purity.

Table 2. Reactivity of 1,3-dimethyl-5-imidazolium-carbaldehyde **1** in different reactions



Reaction and conditions	X	Product	Yield (%)
Knoevenagel[a]		 **5**	54
Wittig[b]		 **6**	50
Schiff base formation[c]		 **7**	95
Base-mediated electrophilic substitution[d]		 **8**	60

[a] Water, rt 30 min.
[b] DCM, rt 20 h.
[c] DCM, rt 4 h.
[d] MeOH, NaOAc, rt 20 h.

Schiff base formation was achieved in DCM by adding a stoichiometric amount of aniline (1.05 equiv) to a suspension of **1** in DCM at room temperature. Product **7** slowly crystallized out of DCM at −20 °C (overnight), providing the desired compound in an excellent yield. For spectroscopic studies, the Schiff base was further recrystallized from DCM.

Fluorescent compound **8** was synthesized via base-mediated electrophilic substitution of 3-(2-carboxyethyl)-1,1,2-trimethyl-1*H*-benzo[*e*]indolium[23] in methanol in the presence of NaOAc. The large Stoke's shift of the fluorescent compound[24] would improve the sensitivity of fluorescence microscopy studies, where the bleeding of excitation light into the detection source can be problematic.

We further demonstrated the oxidation of **1** to a natural product norzooanemonin **9** (Fig. 1). To our knowledge there are only two publications regarding norzooanemonin synthesis. In one of them, the synthesis of **9** was achieved by treating imidazole-4-carboxylic acid with dimethylsulfate.[25] Long reaction times (several days), harsh conditions (100 °C) and a tedious product isolation procedure limit the practical utility of the method. In the second publication, norzooanemonin was prepared by treatment of 1-methylimidazole with dimethyl carbonate.[26] However, attempts to reproduce this method by other investigators yielded 1,3-dimethyl-imidazolium-2-carboxylate instead of the expected 1,3-dimethyl-imidazolium-4-carboxylate.[27] In our method, we found that the reaction of **1** with a relatively mild oxidation reagent chlorite selectively oxidized the aldehyde to the corresponding carboxylic acid. An initial attempt to conduct the reaction in aqueous KH_2PO_4 buffer did not yield the expected product after 24 h. In contrast, the addition of 20 vol % of DMSO to the reaction mixture resulted in 100% conversion within 10 min (Scheme 1, A). The role of DMSO could be rationalized in two ways. First, DMSO could interact with the hypochlorite ion formed in the oxidation process (DMSO is a known hypochlorite ion scavenger[28]), thereby driving the reaction equilibrium to the right. Second, in the presence of DMSO, **1** tautomerizes to its keto-form (Table 1) which is more reactive toward oxidation than the corresponding enol-form. In aqueous solution, **1** is predominantly in its unreactive enol form. Further study to delineate the role of DMSO in this reaction is in progress. Although our approach gave 100% conversion, isolation of the product from salt mixtures was cumbersome and required numerous cycles of methanol–ethanol triturations (inorganic salts are less soluble in methanol–ethanol mixture than **9**). To minimize the presence of inorganic salts and simplify the work-up, we optimized the reaction by conducting the oxidation with chlorite and phosphate immobilized on a solid support[29] (Scheme 1, B). As in method A, the formation of the product in method B was fast (less than 1 h) and quantitative. The NMR spectra of the product matched published data.[25,30]

In all studied reactions, the dimethylated imidazolium survived the reaction conditions, allowing either successful incorporation of a permanent cationic imidazolium moiety into diverse molecules (Table 2) or opening a new route to synthesis of the natural compound norzooanemonin. Considering that dialkylated imidazolium constitute a major class in the rapidly expanding area of ionic liquids and ionic liquid crystals,[31] extension of the use of **1** in material science is conceivable. Similarly, **1** could be used to incorporate dimethylated imidazoles into N-heterocyclic carbenes, which are good chelating groups for a variety of metals used in organometallic catalysis and general organic synthesis.[32] Thus, the availability of a suitable building block for the incorporation of di-*N*-methyl-imidazolium would allow complementing a variety of compound libraries with important functionality.

In conclusion, we demonstrated an efficient synthesis of novel 1,3-dimethyl-5-imidazolium-aldehyde and a known 1,3-dimethyl-2-imidazolium-aldehyde. Both compounds were found to be non-hydroscopic and air stable. We demonstrated the solvent dependent tautomerism of both compounds and showed their utility (using 1,3-dimethyl-5-imidazolium-aldehyde **1** as an example) as synthons for incorporating imidazolium functionality into molecules through a variety of reactions: Knoevenagel condensation, Wittig reaction, Schiff base formation and base-mediated electrophilic substitution. We also demonstrated that **1** can be used for direct synthesis of norzooanemonin via oxidation.

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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.2006.12.051.

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