THE FASCINATING CHEMISTRY OF MESOIONIC 4-TRIFLUOROACETYL-1,3-OXAZOLIUM-5-OLATES AND RELATED COMPOUNDS

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Abstract – This review illustrates the unexpected and unique transformation of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (4-TFMK-münchnones) on treatment with different nucleophiles. A trifluoromethyl group that cannot be synthesized by the usual methods is incorporated in the products. The research discussed in this review is focused on the rich chemistry of 4-TFMK-münchnones. In particular, we highlight the recent advances in their use in contemporary organic synthesis, primarily of trifluoromethyl-substituted heterocycles. The chemistry of related mesoionic compounds is also discussed.

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1. INTRODUCTION

Mesoionic 1,3-oxazolium-5-olate (münchnone) derivative 2 was first synthesized in 1958 by Lawson and Miles¹ by cyclodehydration of 2-pyridone-N-acetic acid 1 with acetic anhydride (Scheme 1, eq. 1). The 1,3-dipolar (azomethine ylide type) reactivity of münchenones 3 was originally discovered by Huisgen in 1964 (Scheme 1, eq. 2).² Since then, the Huisgen group has extensively studied the chemical properties, reactivity, and utility of münchenones 3, the name of which was derived from Huisgen’s alma mater, the Ludwig-Maximilians-Universität München.

Scheme 1. Preparation of münchenones and their 1,3-dipolar cycloaddition reaction

Münchnones 3, synthesized from N-alkyl(aryl)-N-acyl α-amino acids 4, have received steady interest for more than 60 years. In particular, as they are highly reactive 1,3-dipoles, their 1,3-dipolar cycloadditions (known as the Huisgen cycloaddition) have been extensively studied.³ Münchnones can undergo cycloaddition reactions with a range of unsaturated substrates (e.g. alkynes, alkenes, imines, and aldehydes), and this reactivity provides potential access to various classes of heterocycles.⁴ Thus, münchenones, like sydnones,⁵ are one of the most extensively studied classes of mesoionic compounds.⁶
A review by Gribble covering the syntheses, structures, and reactions of münchenones in the literature available up to 2000 appeared in 2003. Recent new aspects of münchenone chemistry, mainly features regarding novel generation method for münchenones were reviewed by Reissig and Zimmer in 2014. The present article is a comprehensive survey of the chemistry of 4-TFMK-münchnones with trifluoroacetyl groups at the 4-position, mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (4-TFMK-münchnones) 5, based primarily on our research results.

Scheme 2. 4-TFMK-münchnones 5 in diversity-oriented synthesis

4-TFMK-münchnones 5 contain numerous reactive sites, allowing a diverse set of possible modifications (Scheme 2). Highly substituted heterocyclic scaffolds can be directly accessed from 5. The diverse reactivity makes them useful synthons for trifluoromethyl-substituted heterocycles. Because of the strong influence of fluorinated groups on the physical, chemical, and biological properties of compounds and the
fact that a large majority of modern medicines and agrochemicals contain one or more heterocyclic rings, trifluoromethyl-substituted heterocycles are of high interest in medicinal, agrochemical, and materials chemistry.\(^7\)

This review is intended to create a prognostic scheme to illustrate the unexpected and unusual transformations of 5 on treatment with different nucleophiles and to partially compare the results with those of non-acylated münchnones.

## 2. 4-TFMK-MÜNCHNONES AND RELATED MESOIONIC COMPOUNDS

### 2-1. Synthesis and properties of münchnones

Although the term “mesionic” has been used to imply a variety of heterocyclic systems, such as six-membered heteroaromatic betaines and heteropentalenes, a consensus is growing that use of this term should be restricted to five-membered heterocycles.\(^8\) This restriction excludes betaines, heteropentalenes, and five-membered heterocyclic N-oxides; however, it does not exclude five-membered rings fused to other heterocyclic systems. Münchnones have a sextet of π electrons and an aromatic character, but their properties and reactivities are very different from those of aromatic compounds. Whether or not münchnones are aromatic is still controversial.\(^9\)

![Scheme 3. Preparation of münchnones 3 from N-alkyl(aryl)-N-acyl α-amino acids 4](image)

In general, münchnones 3 are readily prepared by cyclodehydration of 4 with reagents such as acetic anhydride,\(^2\) \(N,N^1\)-dicyclohexylcarbodiimide (DCC),\(^10\) or \(N\)-ethyl-\(N^1\)-dimethylaminopropylcarbodiimide (EDC)\(^11\) and are utilized in situ because they are too unstable to be isolated (Scheme 3). Only münchnones with aryl substituents at both the 2- and 4-positions or with an acyl group in the 4-position have been isolated.\(^2b\)

Alternative approaches for the formation of münchnones have been reported. In 2000, the novel generation of münchnones from chromium carbene complexes 6 was reported by Merlic and co-workers.\(^12\) Carbene complexes 6 react with carbon monoxide to yield chromium ketene complexes 7, which cyclize to münchnones 8; these are then converted into pyrroles 9 through 1,3-dipolar cycloaddition with alkynes (Scheme 4).
Scheme 4. Cyclization reactions of münchnones 8 generated from chromium carbene complexes 6

Tepe et al. reported the conversion of azlactones 10 by trimethylsilyl chloride (Scheme 5, eq. 1)\(^\text{13}\) or silver acetate (Scheme 5, eq. 2)\(^\text{14}\) into N-metalated münchnone intermediates 11 (\(LA=\text{Me}_3\text{Si}\) or \(\text{Ag}\)), which undergo a 1,3-dipolar cycloaddition in the presence of alkenes.

Scheme 5. Cyclization reactions of \(N\)-metalated münchnones 11 generated from azlactones 10

Toste et al. have also developed a gold-catalyzed conversion route of generating aura-münchnone intermediate 11 (\(LA=(\text{AuOBz})_2L^*\)) from azlactones 10.\(^\text{15}\) Intermediate 11 (\(LA=(\text{AuOBz})_2L^*\)) undergoes regio- and stereoselective 1,3-dipolar cycloadditions with alkenes (Scheme 5, eq. 3).

The Arndtsen group designed three new routes to generate münchnones by multicomponent reactions: (1) the palladium-catalyzed carbonylative coupling of imines, acid chlorides, and carbon monoxide to afford münchnones 12;\(^\text{16}\) (2) the one-pot reaction of imines, acid chlorides and phosphonites to give phospha-münchnones 13 (called montréalones);\(^\text{17}\) and (3) the isocyanide-mediated reaction of imines and acid chlorides to afford imino-münchnones 14 (Scheme 6).\(^\text{18}\) The 1,3-dipoles 12-14 can undergo
cycloaddition with alkynes and alkenes to produce a range of heterocyclic products. Montréalones 13 undergo regio- and enantioselective cycloaddition reactions because the PR₃ moiety in the ring increases the carbanionic character of the adjacent carbon atom and creates a steric bias across the 1,3-dipole.¹⁷

Scheme 6. Münchnones, montréalones, and imino-münchnones generated by one-pot reactions of imines and acid chlorides with either CO/Pd (for 12), PR₃ (for 13), or RNC (for 14)

2-2. Synthesis and properties of 4-TFMK-münchnones and related mesoionic compounds

In 2014, Larock, Shi et al. used the term “stable münchnones” to refer to münchnones with electron-withdrawing groups at the 4-position.¹⁹ Later, Harrity et al. also called them “stabilized münchnones”.²⁰ These münchnones can be significantly more stable than their non-acylated analogs, allowing them to be isolated, purified and used as electrophiles and 1,3-dipoles.

Münchnones with trifluoroacetyl groups at the 4-position, 4-TFMK-münchnones 5, were first synthesized in 1964 by Singh and Singh through the cyclodehydration of N-benzoyl-N-phenylglycine 15 (R¹=R²=Ph).²¹ In 1967, Greco et al. also reported experimental details of the preparation of additional 4-TFMK-münchnones 5 with spectral data.²² The first reported reaction of 5 was the reactions with oxygen nucleophiles.²¹ After 30 years, the synthetic utility of compounds 5 as valuable building blocks for the preparation of trifluoromethyl-substituted compounds was recognized when our group reported the reaction of 5 with amidines to afford 5-trifluoroacetylimidazoles (see Scheme 25).²³

4-TFMK-münchnones 5 are easily prepared from N-acyl-N-alkylglycines 15 in one step through cyclodehydration by trifluoroacetic anhydride followed by trifluoroacetylation at the C-4 position of intermediary mesoionic 1,3-oxazolium-5-olates 16 (Scheme 7).²² Generally, compound 5 can be isolated as crystalline materials and are reasonably stable on the bench top. Compounds with various substituents at the 2- and 3-positions can be synthesized. Of the compounds that we have synthesized, only the
2-methyl-3-phenyl-4-trifluoroacetyl derivative of 5 (R^1 = Ph, R^2 = Me) decomposed very slowly during storage in the refrigerator.

\[ \text{Scheme 7. Preparation of 4-TFMK-münchnones 5 from } N\text{-alkyl(aryl)-N-acyl } \alpha\text{-amino acids 15} \]

The preparation of 4-acetylmünchnones 17 has been described in three papers.\(^{19,24a,b}\) Generally, compounds 17 are isolated and purified by recrystallization, whereas purification by column chromatography was generally problematic. Therefore, preparation of 17 with diverse substituents is difficult.\(^{19}\) Conversely, acylation of 2-pyridone-N-acetic acid 1 with acyl chlorides or anhydrides leads to stable mesoionic 3-acyloxazolo[3,2-\(a\)]pyridinium-2-olates.\(^{1,25}\)

As far as we know, the synthesis of 4-formylmünchnones, among the related 4-acylmünchnones, has not been reported so far (Table 1).

<table>
<thead>
<tr>
<th>Table 1. 4-Acyl mesoionic compounds</th>
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<tbody>
<tr>
<td>R</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>(\text{N}^+\text{O}^-\text{N}^+\text{O}^-\text{R}_1\text{R}_2)</td>
</tr>
<tr>
<td>(\text{CF}_3)</td>
</tr>
<tr>
<td>(\text{CH}_3)</td>
</tr>
<tr>
<td>H</td>
</tr>
</tbody>
</table>

\(^a\) ref. 21 and 27. \(^b\) ref. 19 and 24. \(^c\) ref. 26. \(^d\) ref. 27. \(^e\) ref. 34. \(^f\) ref. 32. \(^g\) ref. 31.

4-Acyl-1,3-thiazolium-5-olate derivatives, such as those with trifluoroacetyl (18),\(^{26}\) acetyl (19),\(^{27}\) and formyl (20)\(^{26}\) substituents, are known compounds. However, their chemistry has not yet attracted much attention.

In 1967, the Huisgen group pioneered cycloaddition reactions of münchnones 3 with carbon disulfide to afford 1,3-thiazolium-5-thiolates (Scheme 8).\(^{28}\) The mesoionic compounds have attracted special attention as nonlinear optical materials because of their large optical hyperpolarizabilities.\(^{29}\) However, 4-acyl-1,3-thiazolium-5-thiolate derivatives have not yet been synthesized (Table 1). In addition, our
attempted preparation of 4-trifluoroacetyl-1,3-thiazolium-5-thiolates by the cycloaddition of 5a (R¹ = Me, R² = Ph) with CS₂ was not successful.³⁰

\[ R^1 = \text{Me}; R^2 = 4-\text{ClC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4; \]
\[ R^3 = \text{Ph}, 4-\text{MeC}_6\text{H}_4, 4-\text{Me}_2\text{CHC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4 \]

Scheme 8. Cycloaddition of münchnones 3 with CS₂ to give 1,3-thiazolium-5-thiolates

Sydnone derivatives substituted with an acyl group at the 4-position were reported to be stable compounds. 4-Formyl- (23)³¹ and 4-acetylsydnones (22)³² were obtained by direct acylation of 4-unsubstituted sydnones 24, whereas 4-trifluoroacetylsydnones 21 were not synthesized by direct trifluoroacylation.³³ In 2017, 4-trifluoroacetyl-3-phenylsydnone 21a (R¹ = Ph) was first synthesized from 3-phenylsydnone 24a (R¹ = Ph) by trifluoromethylation of 4-formyl-3-phenylsydnone 23a (R¹ = Ph) with trifluoromethyltrimethylsilane followed by oxidation with o-iodoxybenzoic acid (IBX) of the corresponding trifluoromethyl alcohol 25a (R¹ = Ph) (Scheme 9).³⁴ In the design of bioactive sydnones, hybrid molecules of sydnones and other heterocycles such as imidazoles have been synthesized from 4-formylsydnones 23 as an attractive starting material.³⁵ The Schmidt reaction of 4-acetylsydnones 22 with sodium azide and sulfuric acid afforded syndonyl-methylamides.³⁶

\[ \text{Ph} + \text{POCl}_3/\text{DMF} \rightarrow \text{Ph} \]
\[ \text{Ph} \rightarrow \text{Ph} \]
\[ \text{Ph} \rightarrow \text{Ph} \]
\[ \text{Ph} \rightarrow \text{Ph} \]

Scheme 9. Preparation of 4-trifluoroacetyl-3-phenylsydnone 21

However, there is much less information about the reactivity of 4-acylated mesoionic 1,3-thiazolium-5-olates, 1,3-thiazolium-5-thiolates, and sydnones in the literature in comparison with 4-TFMK-münchnones 5.
3. CHEMICAL REACTIONS

3-1. Ring-opening reaction

With regard to the electrophilic sites of 5, H$_2$O and ethanol attack at the C-5 position.$^{21}$ Hydrolysis of 5 with H$_2$O results in decarboxylation and the formation of trifluoromethyl ketone hydrates 26 (Scheme 10, eq. 1). Alcoholysis of 5 gives the ring opening products 27 in high yields (Scheme 10, eq. 2). However, an alternative mechanism, in which O-nucleophiles such as H$_2$O and MeOH attack at the C-2 position of 5, has not been ruled out from a comparison of the starting compound and the product. As described in a later section (see Scheme 27), aminolysis of 5 with ammonia proceeds by initial attack at the C-2 position of 5, followed by ring opening, decarboxylation, and cyclization to give 4,5-dihydroimidazoles.$^{37}$

One distinguishing feature between the two possible mechanisms of ring opening of 5 is the source of the oxygen on the amide of product 26 in the case of an attack of O-nucleophiles at C-5 (pathway a) and at C-2 (pathway b) (Scheme 11). By performing the reactions of $^{18}$O-labeled 5a$^*$ with H$_2$O and 5a with H$_2^{18}$O, it should be possible to obtain direct evidence regarding the site of the nucleophilic attack on 5.$^{38}$ 18O-Labeled 5a$^*$ was prepared from N-methyl-N-$[^{18}$O]benzoylglycine, obtained by the Schotten-Baumann reaction of N-methylglycine with $[^{18}$O]benzoyl chloride.

![Scheme 10. Hydrolysis and methanolysis reaction products of 5](image)

![Scheme 11. Hydrolysis of $^{18}$O-labeled 5a$^*$ and 5a](image)
Thus, hydrolysis of 5a* (18O content: 94%) with H2O gave trifluoromethyl ketone hydrate 26a* (18O content: 93%). In the hydrolysis of 5a with H218O, 18O was not incorporated into the amide carbonyl of product 26a. Therefore, it is evident that the reaction proceeds through regioselective attack of H2O on the C-5 position of 5a (pathway a) and not the C-2 position (pathway b), as described by Singh et al.21 These data are consistent with an MO study indicating that N-nucleophiles attack at the C-2 position and O-nucleophiles attack at the C-5 position on the basis of the HSAB theory.38

3-2. Trifluoromethyl-substituted pyrroles

3-2-1. Reaction with enamines

In pioneering work on the 1,3-dipolar cycloaddition of münchnones, Huisgen and co-workers reported that the reaction of münchnones with acetylenes substituted with one or two electron-withdrawing groups can be used to synthesize a great variety of substituted pyrroles (Scheme 1, eq. 2).39 In 1991, the münchnones cycloaddition reaction with trifluoromethylated dipolarophiles 28 to afford β-trifluoromethylpyrrroles 29 was reported (Scheme 12).40

However, because of the strongly electron-withdrawing trifluorooacetoyl group, 4-TFMK-münchnones 5 do not easily undergo 1,3-dipolar cycloaddition reactions with double- or triple-bonded electron-poor dipolarophiles. In fact, 2-ethylthio-3-methyl-4-trifluoroacetoyl-1,3-oxazolium-5-olates with dimethyl acetylenedicarboxylate at 120 °C underwent 1,3-dipolar cycloaddition followed by extrusion of CO2 to afford a pyrrole with a poor yield of 6% (Scheme 13).41 In addition, 3-methyl-2-phenyl-4-trifluoroacetoyl-1,3-oxazolium-5-olate (5a) did not undergo 1,3-dipolar cycloaddition reactions with acetylenic iminium salts; instead, Michael addition and a six-electron electrocyclic ring closure yielded pyranone derivatives (Scheme 14).42
Characteristically, arynes do not react with 5a, whereas 4-acetilmünchnones 17 do undergo a cycloaddition because the acetyl group is less electron withdrawing than the trifluoroacetyl group (Scheme 15). The reaction expands aryne dipolar cycloaddition with 17 to afford mixtures of isoindoles 30 and 9,10-dihydro-9,10-epiminoanthracenes 31, which arise from a second cycloaddition of the aryne and 30.19

In a relatively successful example, Harrity et al. reported that the cycloaddition of 4-TFMK-münchnones 5 with aryl-substituted alkynes gave a good yield of 2-trifluoroacetylpyrroles 32, whereas the reaction with alkyl-substituted alkynes proved to be much less reactive (Scheme 16).20
The cycloaddition reaction of 5 with enamines was successful. Harrity et al. reported a limited number of reactions between 5 and terminal enamines (Scheme 17). In addition, the same reaction was applied to a variety of enamines; it represents a general entry to substituted 2-trifluoroacetylpyrroles 32, proving the usefulness of 1,3-dipolar cycloadditions of 5 with enamines (Scheme 18). During the reaction, addition of trifluoroacetic acid (TFA) increases the yields of the cycloaddition products. Enhanced reactivity and high regioselectivity are also observed in the cycloaddition of 5 with enamines, and the regioselective outcome has been verified through the syntheses of 3,4-disubstituted pyrroles 32. Considering the variety
of enamines that react with 5, this approach can in principle provide access to a range of 2-trifluoroacetylpyrroles 32.

Scheme 19. Mechanism of the reaction of 5 and enamines

The reaction involves a typical 1,3-dipolar cycloaddition to give bicyclic adduct 33 (Scheme 19). Intermediate 33 is protonated by TFA to produce intermediate 34, which releases CO₂ and pyrrolidine to give the pyrrole 32 via intermediate 35. In the reaction, the role of TFA may be to protonate intermediate 33 and facilitate the elimination of pyrrolidine. Another role of TFA could be to trap pyrrolidine produced from the enamines, avoiding the formation of the side products such as 36 (Scheme 19).

Table 2. LUMO and HOMO energies (eV units)\textsuperscript{a} of münchnones and dipolarophiles

<table>
<thead>
<tr>
<th></th>
<th>3a</th>
<th>5a</th>
<th>37</th>
<th>Methyl propiolate</th>
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<tbody>
<tr>
<td>LUMO</td>
<td>–1.905</td>
<td>–2.694</td>
<td>0</td>
<td>–1.823</td>
</tr>
</tbody>
</table>

\textsuperscript{a} DFT calculations at the B3LYP / 6-31+G (d, p) level of theory.
In order to assess the effects of the trifluoroacetyl group at the 4-position in 5, DFT calculations for 5a (R\(^1\) = Me, R\(^2\) = Ph) and 4-unsubstituted münchnone 3a (R\(^1\) = Me, R\(^2\) = Ph) were carried out according to the B3LYP/6-31+G (d, p) method.\(^{45}\) The results are summarized in Table 2 and clearly show the differences in the LUMO and HOMO levels. Calculations were also performed for 1,3-dipolarophiles such as enamine 37 and methyl propiolate. Münchnone 3a, bearing a hydrogen atom at the 4-position, has relatively higher energy levels for the LUMO and HOMO. Thus, the typical 1,3-dipolar cycloaddition of münchnones with electron-poor dipolarophiles is considered to be a HOMO-dipole and LUMO-dipolarophile controlled reaction.\(^{39,46}\)

By contrast, 4-TFMK-münchnone 5a has relatively low energy levels for the LUMO and HOMO. Therefore, the introduction of an acyl function at the 4-position in münchnones usually suppresses cycloaddition with electron-poor dipolarophiles. Conversely, 1,3-dipolar cycloaddition of electron-rich olefins, such as enamines, is expected to be a LUMO-dipole and HOMO-dipolarophile controlled reaction.\(^{47,48}\)

The energy values for the HOMOs/LUMOs of 5a and enamine 37 lead us to believe that the LUMO\(_{\text{dipole}}\)-HOMO\(_{\text{dipolarophile}}\) interaction is prevalent (\(\Delta E = -2.041\) eV versus \(-6.368\) eV for the opposite HOMO–LUMO pair). Thus, the 1,3-dipolar cycloaddition should involve the LUMO of 5 (1,3-dipole) interacting with the HOMO of the enamine (dipolarophile). Therefore, the regioselectivity arises from a combination of two kinds of attractive interactions operating in the transition state and the reaction can proceed through concerted asynchronous mechanisms which were reported in the cycloaddition of nitroethane and electron-rich alkenes.\(^{49}\)

3-2-2. Reaction with P-ylides or S-ylides

The reaction of P-ylides with 5 gives 1,2-disubstituted and 1,2,3-trisubstituted 4-trifluoromethylpyrroles 38 (Scheme 20, eq. 1).\(^{50}\) The reaction begins with P-ylides attacking at the C-2 position of 5 (Scheme 21). In order for this reaction to be successful, it is necessary to add acetic acid or hexafluoro-2-propanol and apply heat after the reaction with ylide. The reason for this is believed to be to facilitate elimination of Ph\(_3\)P=O after the formation of intermediate 40 in the reaction.

Similarly, the reaction of S-ylides with 5 proceeds through nucleophilic addition at the C-2 position to form multisubstituted pyrroles 39 bearing both an alkyl(aryl)thio and a trifluoromethyl group at the 3- and 4-positions (Scheme 20, eq. 2).\(^{51}\) In the reaction, side product 41 is also obtained (Scheme 22). In general, 2- or 5-substituted pyrroles are easily synthesized by aromatic electrophilic substitution, such as trifluoromethylation, whereas a special strategy is necessary to obtain 3- or 4-substituted pyrroles.\(^{52}\) Therefore, these reactions are valuable as synthetic methods for pyrroles with trifluoromethyl groups introduced at the 3- or 4-positions. Together, these reactions provide an effective approach to construct
pyrroles, in which the substitution at any position on the product can be modified by changes to the P- and S-ylides or münchnones 5.

\[
\begin{align*}
R^1 & = \text{Me, Bn, Ph; } R^2 = \text{Me, } t\text{-Bu, Ph, } 4\text{-MeOC}_6\text{H}_4; R^3 = \text{H, Me, Pr, } C_8\text{H}_{17}, \text{ OMe (eq. 1)} \\
R^1 & = \text{Me, Bn, Ph; } R^2 = \text{Me, Ph, } 4\text{-MeOC}_6\text{H}_4 \text{ (eq. 2)}
\end{align*}
\]

Scheme 20. Reactions of 5 with P-ylides or S-ylides

\[
\begin{align*}
\text{Scheme 21. Mechanism for the formation of 4-trifluoromethylimidazoles 38}
\end{align*}
\]
3-3. Trifluoromethyl-substituted imidazoles

3-3-1. Reaction with amidines
Studies by the Huisgen group demonstrated the preparation of imidazoles by treating münchnones with electron-deficient nitriles (Scheme 23). This method involves a 1,3-dipolar cycloaddition reaction of münchnones and affords imidazoles containing electron-withdrawing groups in moderate yields.

Construction of the imidazole scaffold can also be performed by treating münchnones with N-phenylsulfonyl imines (Scheme 24). The procedure involves a 1,3-dipolar cycloaddition reaction and the phenylsulfonyl moiety of the imines is a good leaving group. The Arndtsen group also reported that in situ generated montréalones reacted with N-nosyl imines to give imidazoles. In addition, a palladium-catalyzed synthesis of 2-arylimidazoles by the 1,3-dipolar cycloaddition of in situ generated münchnones with N-tosyl imines was developed by Arndtsen et al.
\[
\text{Me}^+ \text{R}^1 \text{R}^2 \xrightarrow{\text{R}^3 \text{CH} = \text{N SO}_2 \text{Ph}} \xrightarrow{-\text{CO}_2, -\text{PhSO}_2^\cdot} \text{Me}^+ \text{R}^1 \text{R}^2 \text{R}^3
\]

\( R^1 = \text{Me, Ph}; R^2 = \text{Me, Ph}; R^3 = \text{H, Ph, 4-MeOC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4 \)

Scheme 24. 1,3-Dipolar cycloaddition of münchnones with N-phenylsulfonyl imines

The solid-supported synthesis of imidazoles by similar reactions with münchnone generation and cyclization with N-tosyl imines has also been reported.\(^{57}\)

4-TFMK-münchnones 5 react with amidines to afford trisubstituted 5-trifluoroacetylimidazoles 43 in moderate yields (Scheme 25).\(^{23}\) The proposed mechanism, in which the amidines attack at the C-2 position of 5, is illustrated in Scheme 26.

\[
\begin{align*}
\text{R}^1 &= \text{Me, Ph; R}^2 = \text{Me, } t\text{-Bu, Ph} \\
\text{Scheme 25. Reaction of 5 with amidines}
\end{align*}
\]

Hamper and co-workers employed a solid-phase protocol for the generation of a library of 200 5-trifluoroacetylimidazoles based on the reaction of 5 with amidines.\(^{58}\) Trifluoroacetylation of 1-alkyl-substituted imidazoles gave 2-trifluoroacetylimidazoles in good yields.\(^{59}\) Therefore, 5-trifluoroacetylimidazoles 43 seem less likely to be synthesized by other methods.
3-3-2. Reaction with ammonia

4-Trifluoromethylimidazoles 44 are accessible via the reaction of 5 with ammonium acetate in DMF followed by dehydration in two steps (Scheme 27). This aminolysis of 5 with ammonia proceeds by initial attack at the C-2 position of 5, followed by ring opening, decarboxylation, and cyclization to give 4,5-dihydroimidazoles 45 (Scheme 28). Dehydration of product 45 by the reaction of phosphorus oxychloride and pyridine gives 5-unsubstituted 4-trifluoromethylimidazoles 44 in high yields. This reaction is also applicable to the syntheses of 4-pentafluoroethyl and 4-heptafluoropropylimidazoles.37

\[
\text{R}^1 = \text{Me, Bn, Ph; R}^2 = \text{Me, t-Bu, Bn, Ph}
\]

Scheme 27. Reaction of 5 with ammonium acetate

Hydrolysis of 5a affords trifluoromethyl ketone hydrate 26 in 83% yield (Scheme 10, eq. 1).60 When the methanolysis of 5a is performed in MeOH in the presence of TFA, the product α-trifluoroacetyl-N-acylglycine ester 27 is obtained in 91% yield (Scheme 10, eq. 2). The reactions of 26 and 27 with ammonium acetate afford the corresponding 4-trifluoromethylimidazoles 45 and 46, respectively, in moderate yields (Scheme 29).60
The isomeric 5-trifluoromethylimidazoles 47 and 48 were prepared by the reactions of 49 and 50, respectively, with ammonia or primary amines in moderate yields; compounds 49 and 50 were obtained by the reactions of 4-trifluoroacetylazlactone 51 with H2O or MeOH, respectively (Scheme 30). Compound 51 is structurally related to 5 and can be prepared at a high yield by the reaction of N-benzoylglycine and TFAA. However, its synthetic potential has not been fully explored as a CF3 synthon. A close look at the structure of 27 and 50 reveals that these compounds contain a carbon substituted with three different reactive functional groups, such as trifluoromethyl ketones, esters, and amides. In 2012, Moody and co-workers reported that ethyl esters of type 50 could be obtained through the rhodium-catalyzed reaction of ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate and benzamides in low yields (32-43%). Several examples of subsequent cyclizations have afforded CF3-substituted oxazoles, imidazoles, and thiazoles.

3-4. 2(1H)-Pyrazinones and imidazo[1,5-a]pyrazin-8(7H)-ones

3-4-1. Reaction with TosMIC or EtOOCOCH2NC

The reaction of 5 with p-toluenesulfonylmethyl isocyanate (TosMIC) in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) affords 2(1H)-pyrazinones 52 in moderate yields. The origin of the C-2 carbonyl oxygen atom in the product 52a* (R1 = Me, R2 = Ph) was shown to be molecular oxygen by 18O-labeling experiments (Scheme 31). This novel ring transformation reaction
proceeds via an initial attack of TosMIC anions on the C-2 position of 5, opening of the oxazole ring, subsequent cyclization, and autoxidation, which includes oxygenation, cyclization of the resulting peroxy anion, and oxidative cleavage (Scheme 32).

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{O} \\
\text{Ph} & \quad \text{N} \quad \text{O} \\
\text{CF}_3 & \quad \text{O} \\
\text{5a} \quad \stackrel{18\text{O}_2, \text{TosMIC, DBU}}{\longrightarrow} \quad \text{Ph} \quad \text{N} \quad \text{O} \\
& \quad \text{Me} \quad \text{N} \quad \text{O} \\
& \quad \text{Ph} \quad \text{N} \quad \text{O} \\
& \quad \text{CF}_3 & \quad \text{O} \\
& \quad \text{52a*} \quad \text{in DMF}
\end{align*}
\]

**Scheme 31. Formation of 2(1H)-pyrazinones 52a* from 5a**

The reaction with TosMIC gives imidazo[1,5-α]pyrazin-8(7H)-one derivatives 53 as side products. The same ring transformation has been achieved to give 54 by the reaction of 5 with ethyl isocyanoacetate (EtOCOCH₂NC), using the same conditions for the reaction with TosMIC (Scheme 33). However, the reaction with EtOCOCH₂NC does not give the side product. In separate experiments, the reaction of 52a (R¹ = Me, R² = Ph) with TosMIC affords 53 in a high yield. The same reaction of 54 with TosMIC also yields imidazo[1,5-α]pyrazin-8(7H)-one derivative 55a (R¹ = Me, R² = Ph). The C-3 positions of 52 and 54 are electrophilically reactive, being part of an imine system. However, the reaction of 52 or 54 with EtOCOCH₂NC fails to give the product under comparable reaction conditions.

\[
\begin{align*}
\text{R}^1 & = \text{Me, Bn, Ph, 4-MeOC}_6\text{H}_4; \quad \text{R}^2 = \text{Me, t-Bu, Ph, 4-BrC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4
\end{align*}
\]

**Scheme 32. Mechanism for the formation of 2(1H)-pyrazinones 52**
The imidazo[1,5-\(a\)]pyrazin-8(7\(H\))-one derivatives 53 are obtained in high yields in one step by the reaction of 5 with TosMIC when three molar equivalents of the reagent are used (Scheme 33).\(^{64}\)

Scheme 33. Reaction of 5 with TosMIC or ethyl isocyanoacetate

In order to examine the effect of the 4-trifluoroacetyl group in 5, three acyl derivatives, namely the trifluoroacetyl, acetyl, and formyl derivatives, 18-20, of 1,3-thiazolium-5-olates have been subjected to
the same reaction conditions with 5 and TosMIC. As shown in Table 3, the trifluoroacetyl derivative 18 gives the product 52a in higher yields than the acetyl and formyl derivatives 19 and 20.

3-5. Reactions with bis-nucleophiles

3-5-1. Reaction with PhNHNH₂

The reaction of 5 with phenylhydrazine produces three different products 56-58, depending on the nature of the solvent and the reaction temperature (Scheme 34). Thus, in polar DMF, 1,2,4-triazines 56 are obtained by a C-2 attack on the mesoionic form of 5 (Scheme 35, pathway a). However, in refluxing benzene solution, pyrazoles 57 are produced by a C-5 attack of the ring-opened ketene 59 (Scheme 35, pathway b). Finally, in 1,2-dichloroethane, pyrazolones 58 are obtained from an attack on the trifluoromethyl ketone group of 5 (Scheme 35, pathway c). Based on the model, the three modes of regioselective attack by phenylhydrazine are found to provide three different products. However, the reactions of a DMF solution of 5 with other hydrazine derivatives, such as hydrazine hydrate, methylhydrazine, hydrazine carbamate, or tosylhydrazine, produces 1,2,4-triazines in moderate yields. Compound 57a (R₁ = Me) treated with benzoyl chloride in the presence of pyridine gives 5-trifluoromethylpyrazole derivative 60 in 87% yield (Scheme 36, eq. 1). By contrast, isomeric 3-trifluoromethylpyrazole derivative 61 is obtained through dehydration and benzoylation of 58a (R₁ = Me, R₂ = Ph) by reaction with benzoic anhydride in refluxing benzene solution (Scheme 36, eq. 2).

![Scheme 34. Reactions of 5 with phenylhydrazine](image-url)

R₁ = Me, Bn, Ph; R₂ = Me, t-Bu, Ph, 4-BrC₆H₄, 4-MeOC₆H₄
3-5-2. Reaction with NH₂OH

Compounds 5 undergo tandem ring opening and ring closure on addition of hydroxylamine to afford 6-trifluoromethyl-1,2,4-oxadiazin-6-ols 62 in high yields (Scheme 37). In this reaction, initial attack at the C-2 position, ring opening, and extrusion of carbon dioxide are followed by intramolecular cyclization (Scheme 38). The reaction is influenced by the solvent and base. The best result is obtained from the reaction of 5 with hydroxylamine hydrochloride in DMF in the presence of sodium acetate at 80 °C for 3 h. The use of toluene and 1,2-dichloroethane as the solvent diminishes the yield of product. If K₂CO₃ and sodium trifluoroacetate are used as the base, product yields are also reduced.
Scheme 37. Reaction of 5 with hydroxylamine

Scheme 38. Mechanism for the formation of 6-trifluoromethyl-1,2,4-oxadiazin-6-ols 62

3-5-3. Reaction with ortho-substituted anilines

Scheme 39. Reactions of 5 with o-phenylenediamine, o-aminothiophenol, and o-aminophenol

The classical 1,4-binucleophiles o-phenylenediamine, o-aminothiophenol, and o-aminophenol have been introduced into the reaction with 4-TFMK-münchnones 5. The reactions of 5 and o-phenylenediamine
or \( o \)-aminothiophenol give adducts that undergo further cyclization to 1,5-benzodiazepines 63 or 1,5-benzothiazepines 64, respectively (Scheme 39). The reaction of 5 and \( o \)-aminophenol gives adducts 65, derived from a condensation reaction between the amino group of \( o \)-aminophenol and the C-5 atom of 5 (Scheme 39).

3-5-4. Reaction with diethyl aminomalonate

The reaction of 4-TFMK-münchnones 5 with diethyl aminomalonate proceeds in AcOH to give pyrrolidines 66 in moderate yields (Scheme 40).\(^6^8\) If aprotic solvents such as DMF and benzene are used, no characterized product is obtained. The role of AcOH as the solvent may be to facilitate the formation of keto form 67 in the münchenone (Scheme 41). The reaction of product 66 with Ac\(_2\)O in the presence of pyridine affords (2\( H \))-pyrrole 68, which is converted into the highly substituted pyrrole ester 69 by LiOH hydrolysis followed by decarboxylation (Scheme 42). Attempts to condense 5 with ethyl glycinate or \( N \)-methylglycinate have been unsuccessful as a result of the less acidic methylene group relative to that of amino malonate.

\[
\begin{align*}
\begin{array}{c}
\text{Scheme 40. Reaction of 5 with diethyl aminomalonate} \\
R^1 = \text{Me, Bn, Ph}; R^2 = \text{Me, Ph, 4-MeOC}_6\text{H}_4
\end{array}
\end{align*}
\]
Scheme 42. Conversion of 66 into pyrrole 69

3-6. Reaction with P-nucleophiles

Trialkyl phosphites have been evaluated as phosphorus nucleophiles for the addition reaction of 4-TFMK-münchnones 5, thereby producing tetravalent phosphorus zwitterions 70 in good yields (Scheme 43).69 Among the trialkyl or triaryl phosphines tested (including PBu₃, P(t-Bu)₃, PCy₃, and PPh₃), PBu₃ has been found to be the only successful reagent. We speculate that PPh₃, P(t-Bu)₃, and P(C₆H₁₁)₃ are sterically hindered and not sufficiently nucleophilic toward the mesoionic ring. By contrast, PBu₃ is less sterically hindered and functions as a better nucleophile.⁷₀

![Chemical Structure]

**Scheme 43. Reaction of 5 with PBu₃**

Triethyl phosphite, (EtO)₃P, and diethyl phosphite, (EtO)₂P(=O)H, have also been evaluated as P-nucleophiles for addition to 5. In these reactions, starting material 5 is not recovered and several materials are detected by TLC, none of which has been characterized.

The first example of a novel class of acylphosphonium enolates has become readily available in good yields. We have isolated and characterized some stable acylphosphonium zwitterions that are some of the key intermediates in the PBu₃-catalyzed homodimerization of ketoketenes.⁷₀

The mechanism has not yet been elucidated in detail; however, the three possibilities are as follows: (1) Bu₃P attacks the tautomeric intermediate 67 to give the resonance-stabilized zwitterionic compounds 70 (Scheme 44, pathway a); (2) Bu₃P attacks ketene intermediate 58 to give 70 because mesoionic 5 is in equilibrium with the ketene in which the ketene carbonyl group is attacked by Bu₃P (Scheme 44, pathway b); (3) Bu₃P acts as a nucleophilic trigger and forms zwitterionic intermediate 71, which is attacked by a
second Bu$_3$P to give the ring-opening product 70, concomitant with regeneration of Bu$_3$P (Scheme 44, pathway c).

Scheme 44. Mechanism for the formation of acylphosphonium zwitterions 70

Scheme 45. Formation of enol esters 72 from acylphosphonium zwitterions 70

Acylphosphonium zwitterions 70 have been treated with acyl chloride, and the novel formation of trifluoromethylated enol esters 72 has been observed (Scheme 45).
4. CONCLUSIONS

Our development of one-pot, tandem and domino reactions has greatly enhanced the applicability of 4-TFMK-münchnones 5 as valuable CF$_3$ synthons for CF$_3$-substituted heterocycles. The introduction of a trifluoroacetyl group at the 4-position of münchnones enhances the stability of the münchnones and allows them to react with various nucleophiles. In principle, the addition of nucleophiles to 5 can a priori be expected to occur at three different positions (C-2, C-5, or COCF$_3$). In general, N-nucleophiles, such as ammonia and amidines, attack at the C-2 position of 5. Phenylhydrazine demonstrates the remarkable ability to attack at three different positions, depending on the reaction conditions.

The principal advantage of using 4-TFMK-münchnones 5 is the great variety of substituents that are available for R$^1$ and R$^2$. This substituent flexibility in 5 will be reflected in the corresponding substitution of the product. Conversely, 4-TFMK-azlactones 51 may be available as synthetic synthons for CF$_3$-substituted compounds with substitution patterns that cannot be synthesized by 4-TFMK-münchnones.

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