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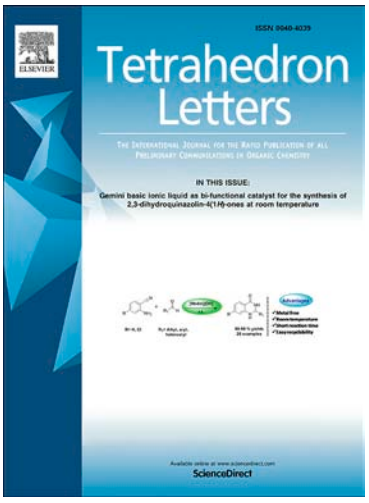


# Reinvestigation of the reaction between aromatic aldehydes, 3-phenyl-5-isoxazolone and sarcosine: stabilized azomethine ylides as a synthetic equivalent of the methylaminomethyl anion

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## Graphical Abstract

**Reinvestigation of the reaction between aromatic aldehydes, 3-phenyl-5-isoxazolone and sarcosine: stabilized azomethine ylides as a synthetic equivalent of the methylaminomethyl anion**

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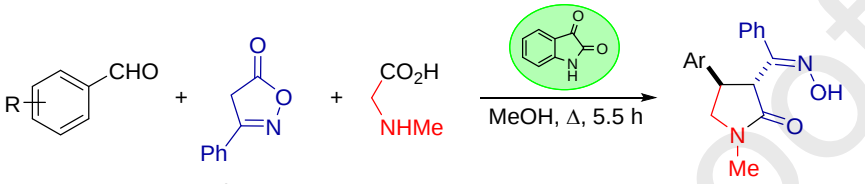


R = H, 4-Me, 4-F, 4-Cl, 4-Br, 4-$CF_3$, 4-$NO_2$, 3-$NO_2$, 4-MeO, 3-MeO, 2-EtO, 3,4-$(MeO)_2$, 3,4-(CH=CH–CH=CH)

13 examples
38–72% yield

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# Reinvestigation of the reaction between aromatic aldehydes, 3-phenyl-5-isoxazolone and sarcosine: stabilized azomethine ylides as a synthetic equivalent of the methylaminomethyl anion

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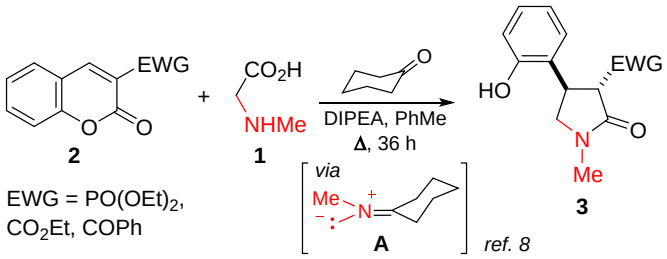
ABSTRACT

The reaction of aromatic aldehydes, 3-phenyl-5-isoxazolone and sarcosine proceeds smoothly at reflux in methanol to give (*Z*)-4-arylidene-3-phenylisoxazol-5(4*H*)-ones, whereas the addition of isatin to the reaction mixture changes the result, providing oximes of 4-aryl-3-benzoyl-1-methylpyrrolidin-2-ones in 38–72% yield.

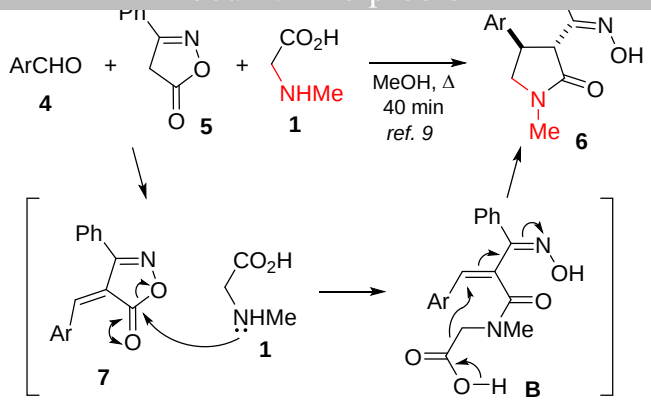


Azomethine ylides are one of the most widely used 1,3-dipoles in organic chemistry.[1] Their major application is the [3+2]-cycloaddition with electron-deficient dipolarophiles leading to functionalized pyrrolidines and oxazolidines.[2] At the same time, the chemistry of azomethine ylides is not limited to the classical [3+2]-cycloaddition. In recent years, there have been many examples of the use of azomethine ylides to obtain unusual pyrrolidines,[3] functionalized piperidines,[4] open-chain alkylamines,[5] and other azaheterocycles.[6] In particular, our group is developing the application of nonstabilized azomethine ylides as synthetic equivalents of an alkylaminomethyl anion.[7]

In 2012, we discovered the direct methylaminomethylation of electron-deficient alkenes with sarcosine (**1**) in the presence of cyclohexanone.[8] In this reaction, coumarins **2** or diethyl benzylidenemalonate provided 4-aryl-2-pyrrolidones **3** *via* the intermediate formation of nonstabilized azomethine ylide **A** (Scheme 1). Our attention was attracted by a paper published by Lakshmi and Perumal in 2013, in which aromatic aldehydes **4**, 3-phenylisoxazolone **5** and sarcosine (**1**) gave related arylpyrrolidones **6** under reflux in methanol (Scheme 2).[9] This reaction seemed to be an unprecedented example of the introduction of a methylaminomethyl anion to the intermediate 4-arylideneisoxazolones **7** in a protic solvent. It was unclear if this reaction was related to our synthesis of pyrrolidones **3** proceeding *via* azomethine ylide formation. A hypothetical azomethine ylide could arise only from the starting aromatic aldehyde and sarcosine. However, to the best of our knowledge, such nonstabilized ylides would be protonated by methanol rather than reacting with **7**.[3b,6f] On the other hand, the authors proposed a non-ylide mechanism, which included the nucleophilic opening of isoxazole ring **7** by sarcosine. The resulting amido acid **B** was decarboxylated, followed by Michael addition of the formed anion at the conjugated double bond (Scheme 2).

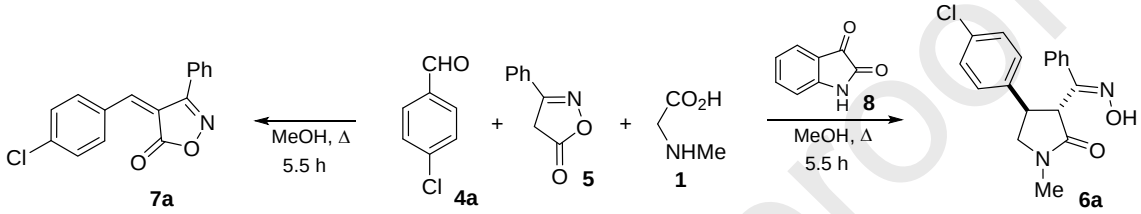



**Scheme 1.** Domino reaction leading to 4-arylpyrrolidones **3**.




**Scheme 2.** Domino reaction leading to 4-arylpyrrolidones **6**.

**Table 1.** Optimisation of the reaction conditions.




| Entry | Isoxazolone **5** (equiv.) | Sarcosine (**1**) (equiv.) | Isatin **8** (equiv.) | Solvent | Time | Yield **7a** (%) | Yield **6a** (%) |
|---|---|---|---|---|---|---|---|
| 1 | 1.00 | 1.00 | 0 | MeOH | 40 min | 61 | 0 |
| 2 | 1.35 | 1.70 | 0 | MeOH | 5.5 h | 64 | 0 |
| 3 | 1.00 | 1.00 | 0.25 | MeOH | 40 min | trace | 47[a] |
| **4** | **1.15** | **1.50** | **0.25** | **MeOH** | **5.5 h** | **0** | **72** |
| 5 | 1.15 | 1.50 | 0.50 | MeOH | 5.5 h | 0 | 68 |
| 6 | 1.15 | 1.50 | 0.10 | MeOH | 5.5 h | 0 | 42 |
| 7 | 1.35 | 1.70 | 0.25 | MeOH | 5.5 h | 0 | 54 |
| 8 | 1.15 | 1.50 | 0.50 | EtOH | 3.5 h | 0 | 55 |
| 9 | 1.35 | 2.10 | 0.50 | EtOH | 3.5 h | 0 | 65 |

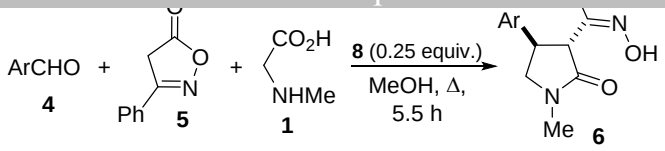
[a] The product was contaminated by the intermediate arylideneisoxazolidinone **7a**.

We were unable to find examples of such facile decarboxylation of amido acids in the literature. On the contrary, their photodecarboxylation is more expected.[10] From any point of view, the reaction described by Lakshmi and Perumal represented a unique and unobvious transformation. However, when we tried to repeat the reaction using a mixture of *p*-chlorobenzaldehyde **4a**, 3-phenylisoxazolone **5** and sarcosine (**1**) the reaction did not lead to pyrrolidone **6a**, but to the arylidene derivative **7a** in 61% yield (Entry 1, Table 1). The use of excess isoxazolone (1.35 equiv.), sarcosine (1.70 equiv.) and an increased time (5.5 h) did not change the result (Entry 2).

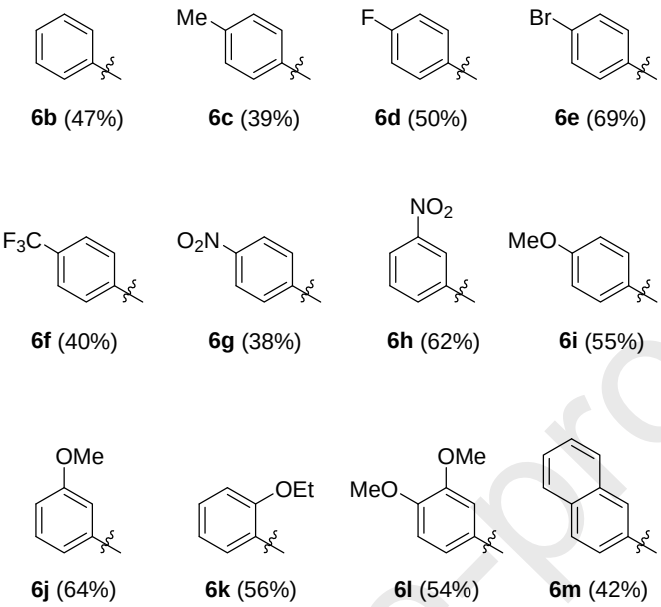
At the same time, it is well-known that stabilized azomethine ylides can react in methanol. Among them, an ylide derived from sarcosine and isatin (**8**) is one of the most widely utilized. Bearing in mind that Lakshmi and Perumal were extensively applying isatin in their other work at the time,[11] we hypothesized that trace amounts of isatin may have been present in the reaction mixture. To our delight, the addition of 0.25 equivalents of isatin changed the result, and, indeed, the major product was pyrrolidone **6a** contaminated by arylideneisoxazolidinone **7a** (Entry 3). Prolonging the time (5.5 h) and utilising excess isoxazole **5** (1.15 equiv.) and the amino acid (1.50 equiv.) increased the yield to 72% and gave pure 4-arylpyrrolidone **6a** (Entry 4). Neither an increase (Entry 5) nor a decrease (Entry 6) in the amount of isatin improved the yield. The application of a larger quantity of isoxazole **5** and sarcosine also did not lead to a better result (Entries 7 and 8). We also found that the reaction proceeded in 95% ethanol to give pyrrolidone **6a** in 55–65% yield (Entries 8 and 9).

We successfully carried out this reaction on a wide range of aromatic aldehydes containing both electron-donating and electron-withdrawing substituents. The position of a substituent in the starting aldehyde did not affect the reaction. On the other hand, in the case of highly electron-rich 2,4-dimethoxybenzaldehyde the intermediate, and less reactive, arylidene derivative **7** was isolated. (Table 2). Products containing Me, Cl, Br, or $NO_2$ groups at the *para* position of the benzene ring crystallized directly from the reaction mixture. At the same time, compounds containing an unsubstituted phenyl ring, *p*-F, *m*-$NO_2$ or alkoxy groups did not crystallize from methanol and were isolated by the extraction of an aqueous-methanolic mixture with dichloromethane followed by crystallization from $CH_2Cl_2$–$C_6H_{14}$.

**Table 2.** Products obtained and their yields.

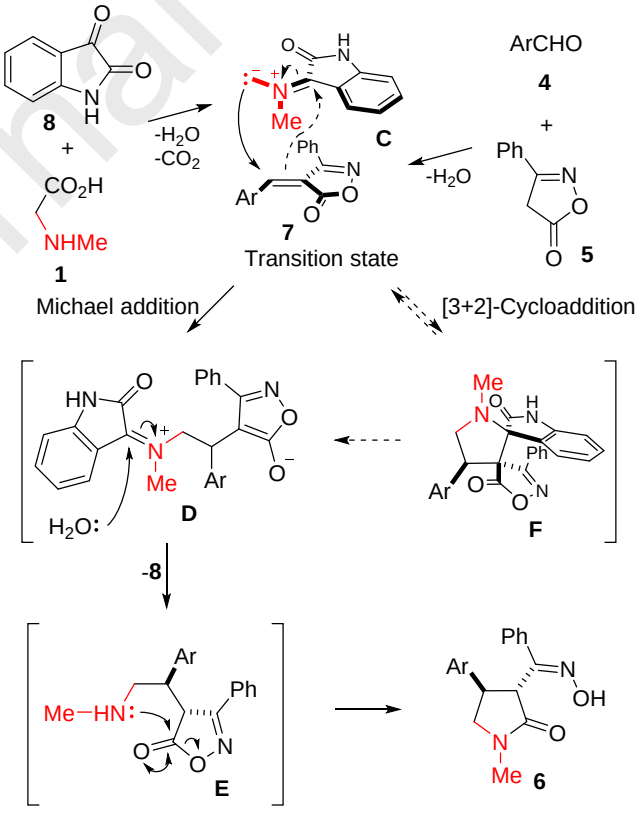



*Aryl groups and yields of pyrrolidones **6***:




The $^1$H NMR data of product **6m** matched that previously reported.[9] Its relative stereoconfiguration was determined using X-ray analysis.[9]

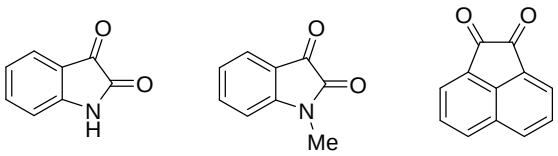
Considering a possible mechanism for the formation of pyrrolidones **6**, we undertook an experiment in which the starting isoxazolone **5** and benzaldehyde **4a** were replaced by 4-(4-chlorobenzylidene)isoxazolone **7a**. As a result, the reaction proceeded smoothly to give the final pyrrolidone **6a** in 62% yield. In view of this, it can be assumed that 4-arylideneisoxazolone **7** is formed at the first stage of the domino-sequence as a result of the Knoevenagel condensation of the




**Scheme 3.** Plausible reaction mechanism.

stabilized azomethine-ylide **C**, which participates in Michael addition with its more accessible terminal carbon at the conjugated bond of the arylidene derivative **7** to provide zwitterion **D**. The latter undergoes hydrolysis to form secondary amine **E** followed by a recyclization yielding the final pyrrolidone **6**. The possibility of the classical [3+2]-cycloaddition of ylide **C** with the electron-deficient alkene **7** cannot be ruled out. In this case, the subsequent cleavage of a strained C–C bond between the electron-withdrawing groups in adduct **F** and the formation of the same intermediate **D** can take place. Rare examples of pyrrolidine ring-opening in cycloadducts are known in the literature.[12] It should be noted that our attempt to obtain adduct **F** at room temperature was unsuccessful. Only pyrrolidone **6a** was isolated in 45% yield after stirring equimolar amounts of isatin, sarcosine, 4-chlorobenzaldehyde and isoxazolone in methanol for 5 days. It was also impossible to obtain adduct **F** from arylideneisoxazolone **7a**, sarcosine (**1**) and isatin (**8**) at reflux in a mixture PhMe–DMF with a Dean-Stark trap to remove the water formed which, presumably, hydrolyzes intermediate **D**. This reaction led to a difficult to purify mixture of at least of seven compounds and traces of pyrrolidone **6a**.

We were also interested in whether compounds other than isatin would be able to initiate the methylaminomethylation of arylideneisoxazolones **7** by sarcosine. We screened a number of carbonyl compounds and found that *N*-methylisatin and acenaphthoquinone also promoted this reaction (Scheme 4). At the same time, ninhydrin, benzil, ethyl phenylglyoxylate and phenyl trifluoromethyl ketone proved fruitless.




yield of **6a**: 72% 63% 41%

**Scheme 4.** Promoters of the reaction.

Finally, we examined the reaction with alkenes, whose [3+2]-cycloaddition with ylide **C** was previously not documented in the literature. We examined widely available diethyl benzylidenemalonate, 3-ethoxycarbonylcoumarin, and a mixture of Meldrum's acid with 4-chlorobenzaldehyde (**4a**), but these reactions did not give the corresponding pyrrolidones. Although Lakshmi and Perumal[9] have reported that proline reacts in a similar manner to sarcosine, we could not reproduce these reactions. As a result, complex mixtures of compounds were formed from which we were unable to isolate or detect the corresponding pyrrolizidinones.

Notably, the obtained pyrrolidones **6a–m** contain phenethylamine and 4-aryl-2-pyrrolidone moieties, which are known to possess valuable biological activities.[13] Related pharmaceuticals, showing anxiolytic and nootropic effects, are Phenylpiracetam (Phenotropil)[13b] and the open-chain amino acid Phenibut.[13a]

In summary, we found that sarcosine can indeed be used to introduce a methylaminomethyl moiety into the 4-arylideneisoxazolone structure to form the 4-aryl-2-pyrrolidone framework. This domino-sequence proceeds only in the presence of dicarbonyl compounds such as isatin, *N*-methylisatin or acenaphthoquinone. The most likely intermediates of this reaction are stabilized azomethine ylides, which makes it an unprecedented case of using these ylides as synthetic equivalents of the methylaminomethyl anion in a protic medium. Further investigation of these reactions is currently underway in our laboratory and will be reported in due course.

## Acknowledgments

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**Supplementary data**

Supplementary data associated with this article can be found in the online version.

## Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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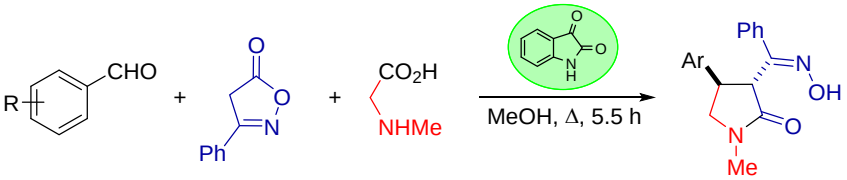


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