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Graphical Abstract

Double decarboxylative route to 3-substituted pyrrolidines: reaction of monoalkyl malonates and related carboxylic acids with sarcosine and formaldehyde

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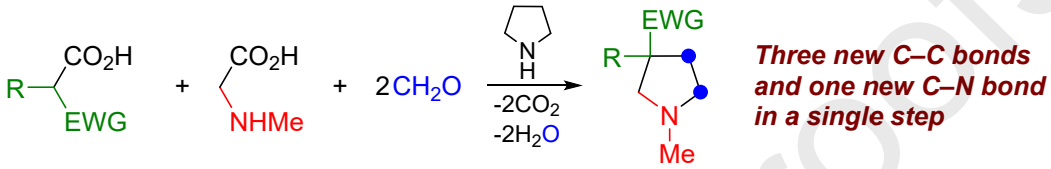

EWG = CO_2R, CN, ArCO, Ac; R = Alk, Ar, H 17–97% yield

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Double decarboxylative route to 3-substituted pyrrolidines: reaction of monoalkyl malonates and related carboxylic acids with sarcosine and formaldehyde

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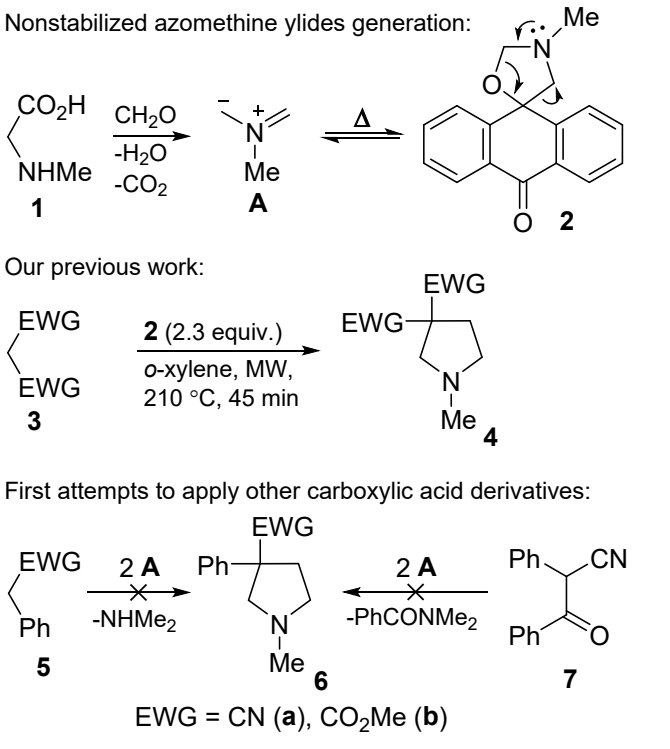
ABSTRACT

Three-component reactions of monoalkyl malonates, cyanoacetic acids or 2-ketocarboxylic acids, *N*-methylglycine, and formaldehyde were developed to rapidly access 3-substituted pyrrolidines in 17–97% yield. These reactions represent a double decarboxylative domino-sequence promoted by pyrrolidine and involve *N*-methylazomethine ylide as the reactive intermediate.

The pyrrolidine ring is a well-known structural moiety in organic chemistry which is also widely distributed in Nature.[1] In view of the biological activities of pyrrolidine alkaloids, this azaheterocycle represents a valuable building-block in pharmaceutical chemistry.[2] One of the most straightforward methods for the synthesis of pyrrolidine derivatives is the [3+2]-cycloaddition of azomethine ylides with electron-deficient alkenes.[3] The advantages of this methodology include the formation of two new C–C bonds in one stage frequently proceeding with high stereoselectivity using inexpensive starting materials. In particular, azomethine ylides can be generated *in situ* from readily available amino acids and carbonyl compounds.[4]

Nonstabilized azomethine ylides are known to be sensitive to the presence of protic compounds in the reaction media such as water or Brønsted acids, which can prevent cycloaddition to the multiple bonds of dipolarophiles.[5] Specifically, our group has investigated the reactions of *N*-methylazomethine-ylide **A**, derived from sarcosine (*N*-methylglycine) (**1**) and formaldehyde, with C=C dipolarophiles possessing CH, NH and OH acidic groups.[6] Recently, we discovered the domino reaction of ylide **A** generated from spiro[anthracene-oxazolidine] **2** with methylene active compounds **3** that resulted in the formation of pyrrolidines **4** in one synthetic step (Scheme 1).[7] The latter are attractive building-blocks in medicinal chemistry but are difficult to synthesize by other methods.[2d,f,8] We were impressed by the effectiveness of this approach and therefore commenced a search of other ways to apply various CH-acidic compounds. Initially, aliphatic ketones were selected as substrates but an attempt to directly carry out their reaction with azomethine ylide precursors failed. However, the application of Mannich bases, obtained from ketones, as starting substrates turned out to be a solution to this obstacle.[9] Recently, we have reported a related domino reaction of branched aliphatic aldehydes.[10]



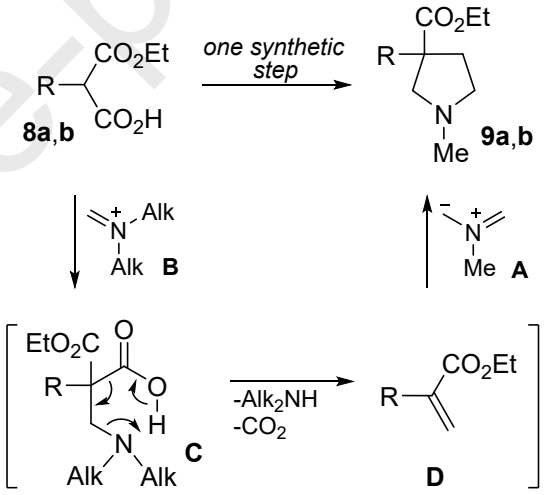
Scheme 1. Reactions between methylene active compounds and *N*-methylazomethine ylide.

derivatives of carboxylic acids, such as esters or nitriles, seemed to be an unreachable challenge. Experiments carried out on benzyl cyanide and phenyl acetate **5**, which possess the most pronounced CH-acidity in this class of compounds, did not provide the desired pyrrolidine **6**. Although we previously observed the retro-Claisen reaction as a side-process in the synthesis of **4**,[7] an attempt to use keto-nitrile **7** for the synthesis of pyrrolidine **6** also failed.

On the other hand, the concept of applying an activating leaving group is particularly attractive for these reactions. One of the most widely investigated leaving groups is the carboxyl group.[11] Thus, we turned our attention to α-monosubstituted malonic acid half esters.[12] These compounds possess a carboxylic group which could be eliminated in the form of carbon dioxide after accomplishing its functions. It is worth noting that the intermediate formation of amino acid **C** should promote a subsequent elimination of dialkylamine and the rapid formation of alkene **D** needed for the final cycloaddition reaction (Scheme 2). In view of the above, only two questions raised doubts. Firstly, would the monoalkyl ester decompose before the azomethine ylide formation? Secondly, would the intermediate amino acid **C** be formed under the reaction conditions?

To test the feasibility of this idea we performed the model reaction of monoethyl benzylmalonate **8a** with an excess of *N*-methylazomethine ylide **A** generated from sarcosine and paraformaldehyde (Scheme 2). To our delight, ethyl 3-benzylpyrrolidine-3-carboxylate **9a** was formed in 74% yield upon heating the reagents at reflux in benzene for 3 h (Table 1, entries 1 and 2). Considering the probable mechanism of this reaction we assumed that azomethine ylide **A** is initially protonated and then acts as a source of iminium cation **B** (Alk = Me) to form acidic Mannich adduct **C**, which further eliminates dimethylamine. From another point of view, due to the presence of formaldehyde in the reaction media it seemed possible to utilize another secondary amine for the generation of the intermediate iminium cation **B** (Alk = Et). We envisioned that higher boiling diethylamine should lead to an improvement in the reaction efficiency. Pleasingly, the three-component reaction mediated by diethylamine provided 3-benzylpyrrolidine **9a** in almost quantitative yield (Table 1, entry 3).

Next, we examined C-ethyl substituted malonate **8b** under the optimized conditions found for benzylmalonate **8a**, but the yield of pyrrolidine **9b** was low (Entry 5). The utilization of *N*-methylazomethine ylide as a source of the iminium cation gave 3-ethylpyrrolidine **9b** in 29% yield (Entry 6). A better result was obtained using pyrrolidine (38%, entry 7). One can assume that associated not only with higher accessibility of the generated iminium cation **B** (Alk = $(CH_2)_4$), but with the higher nucleophilicity of pyrrolidine itself. The latter may have a significant role, since we used the starting formaldehyde in the form of a polymer, while its reaction with a secondary amine initiates the domino sequence. It can be expected that in the case of insufficient rate of the formation of cations **B**, the starting acid **8b** could decarboxylate before the reaction. Given the above, we examined sequential addition of the reagents for the separation of alkene **D** formation and the subsequent [3+2]-cycloaddition. However, the addition of 37% aqueous formaldehyde and pyrrolidine as a source of iminium cation, reflux for 30 min, and subsequent addition of sarcosine and paraformaldehyde led to an insignificant improvement of the yield (41%, entry 8). Notably, the first stage of the reagents addition sequence is important and initial mixing of 37% aqueous formaldehyde and substrate **8b** decreased the yield of pyrrolidine **9b** (Entry 9). An attempt to perform the reaction in a mixture of DMF and benzene in order to improve the solubility of sarcosine, and, consequently, to increase the reaction rate, was unsatisfactory (Entry 10). Thus, optimal reaction conditions for the synthesis of 3-ethylpyrrolidine **9b** were the use of sarcosine and paraformaldehyde in the presence of pyrrolidine at reflux in benzene with a Dean-Stark trap for 3 h (Entry 7).



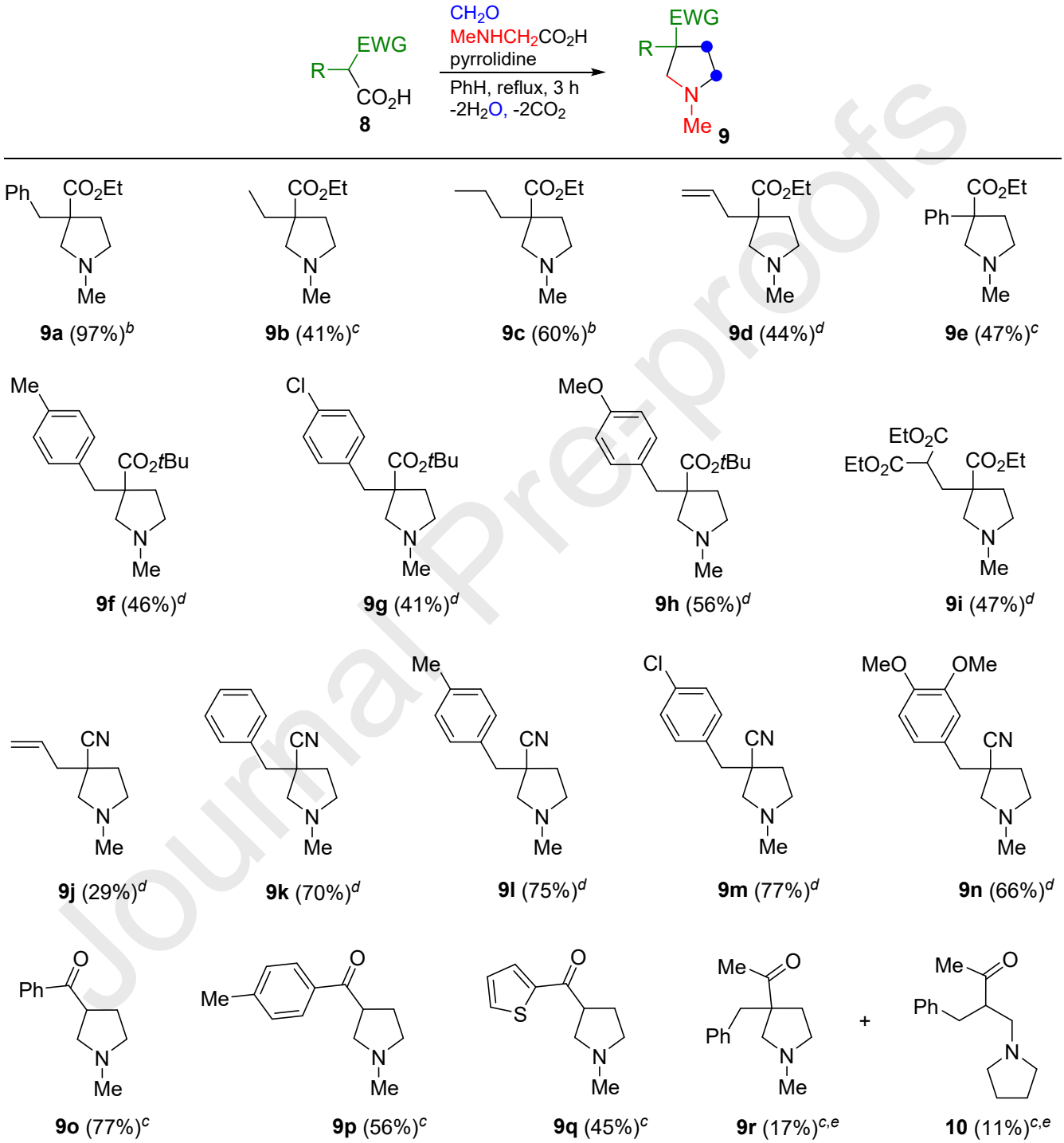
Scheme 2. Pyrrolidination of monoethyl malonates **8a,b**.

Table 1. Optimisation of the reaction conditions.

Entry	R	Reagents (equiv.)	Source of iminium cation **B**	Yield **9a**,**b** (%)
1	Bn	sarcosine (3.0), $(CH_2O)_n$ (5.0)	**A**	74
2	Bn	sarcosine (2.5), $(CH_2O)_n$ (4.0)	**A**	75
3	Bn	sarcosine (1.5), $(CH_2O)_n$ (2.0), Et_2NH (1.0)	$Et_2NH + CH_2O$	97
4	Bn	sarcosine (1.5), $(CH_2O)_n$ (2.0), Et_2NH (0.5)	$Et_2NH + CH_2O$	73
5	Et	sarcosine (1.5), $(CH_2O)_n$ (2.0), Et_2NH (1.0)	$Et_2NH + CH_2O$	21
6	Et	sarcosine (3.3), $(CH_2O)_n$ (5.5)	**A**	29
7	Et	sarcosine (1.5), $(CH_2O)_n$ (3.5), pyrrolidine (1.0)	pyrrolidine + CH_2O	38
8	Et	1) 37% CH_2O_{aq} (1.05); 2) pyrrolidine (1.0); 3) acid **8b**, reflux 0.5 h; 4) sarcosine (1.3), $(CH_2O)_n$ (1.9)	pyrrolidine + CH_2O	41
9	Et	1) acid **8b**; 2) 37% CH_2O_{aq} (1.05); 3) pyrrolidine (1.0), reflux 0.5 h; 4) sarcosine (1.3), $(CH_2O)_n$ (1.9)	pyrrolidine + CH_2O	25
10	Et	acid **8b**, 37% CH_2O_{aq} (1.05), $(CH_2O)_n$ (1.9), pyrrolidine (1.0), sarcosine (1.3), PhH–DMF (1:1)	pyrrolidine + CH_2O	20

monoalkyl malonates utilizing the optimized conditions found for **9b**. Propyl and allyl pyrrolidines **9c**,**d** were synthesized in 60% and 44% yield, respectively. Gratifyingly, 3-ethoxycarbonyl-3-phenylpyrrolidine **9e** which was inaccessible during our preliminary experiments (Scheme 1) was successfully obtained from monoethyl phenylmalonate in 47% yield. Sterically hindered *tert*-butyl benzylmalonates were also utilized in the in 41–56% yield. Notably, partially hydrolyzed methylene-linked diethyl malonate bearing three ester, and one carboxyl groups and therefore two potential reaction centers, selectively formed only pyrrolidine **9i** in 47% yield. This result pointed to a decisive role of the carboxyl moiety as a directing group in the pyrrolidination of CH-acidic substrates.

Table 2. One-step synthesis of pyrrolidines from substituted acetic acids.[a]



[a]Reactions were performed on 1.0 mmol of **8**. Isolated yields based on starting acids **8** are depicted.

[b]**8** (1.0 mmol), sarcosine (1.5 mmol), $(CH_2O)_n$ (2.0 mmol of CH_2O), Et_2NH (1.0 mmol), PhH, Δ, 3 h.

[c]37% CH_2O_{aq} (1.05 mmol), pyrrolidine (1.0 mmol), acid **8** (1.0 mmol), PhH, Δ, 0.5 h; then sarcosine (1.3 mmol), $(CH_2O)_n$ (1.9 mmol of CH_2O), Δ, 3 h.

[d]**8** (1.0 mmol), sarcosine (1.5 mmol), $(CH_2O)_n$ (3.5 mmol of CH_2O), pyrrolidine (1.0 mmol), PhH, Δ, 3 h.

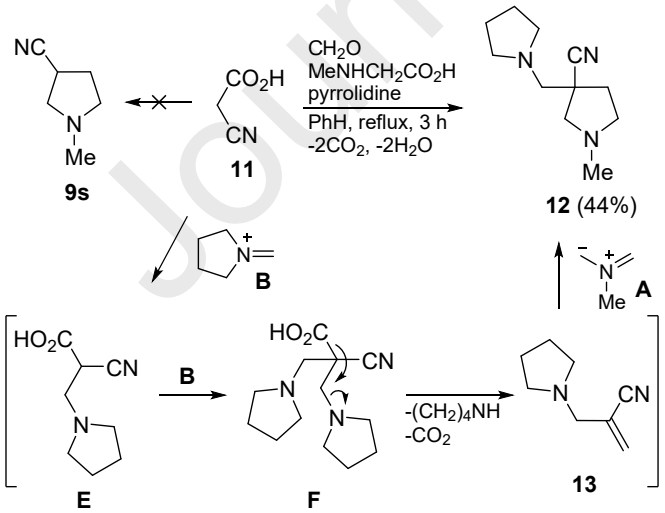
[e]Products **9r** and **10** were obtained as a mixture and separated by column chromatography.

application of C-substituted cyanoacetic acids. Thus, difficult to access 3-alkyl-3-cyanopyrrolidines **9j**–**n** were obtained in moderate to good yields *via* this one-step synthetic protocol.

Encouraged by previous results, we turned our attention to *β*-ketoacids. Noteworthy, the latter possess the highest CH-acidity and the least stability among all of the substrates examined above. The reaction of benzoyl acetic acid with sarcosine, paraformaldehyde, and pyrrolidine only led to a 46% yield of 3-benzoylpyrrolidine **9o**. This result required us to implement a two-step approach (Table 1, entry 8) applying 37% aqueous formaldehyde and pyrrolidine as an iminium cation source. Pleasingly, this modification gave the desired pyrrolidine **9o** in 77% yield. 3-Toluoyl- and 3-thenoylpyrrolidines **9p** and **9q** were obtained in 56% and 45% yield, respectively. In addition, the reaction of 2-acetyl hydrocinnamic acid provided a mixture of 3-acetylpyrrolidine **9r** and Mannich adduct **10** which were separated by column chromatography.

The fact that Mannich base **10** was less reactive under the reaction conditions indirectly provides evidence for the general mechanism of these reactions depicted in Scheme 2. This process therefore includes simultaneous decarboxylation and elimination of dialkylamine from intermediate **C** *via* a six-membered transition state. We also used the Mannich base obtained from acetophenone, formaldehyde and pyrrolidine for the synthesis of pyrrolidine **9o**. However, only trace amounts of pyrrolidine **9o** were formed in a complex mixture of products. Thus, the activating carboxylic acid group implements three functions in the starting substrates **8**: increases CH-acidity, promotes the dialkylamine elimination, and ultimately leaves.

We were curious to investigate the reaction of unsubstituted cyanoacetic acid **11** in the developed methodology. Unexpectedly, dipyrrolidine **12** was formed in 25% yield with no traces of the expected 1-methyl-3-cyanopyrrolidine **9s** (Scheme 3). To promote this unusual reaction we used an excess of pyrrolidine and paraformaldehyde that resulted in 3-(pyrrolidin-1-ylmethyl)pyrrolidine-3-carbonitrile **12** in 44% yield. Moreover, we managed to isolate an unconsumed intermediate of this reaction, 2-(pyrrolidin-1-ylmethyl)acrylonitrile **13** in 15% yield. These facts indicate that the rapid double Mannich reaction of cyanoacetic acid occured before decarboxylation and the elimination of pyrrolidine. These observations are consistent with the general mechanism of the reaction and the formation of amino acidic intermediates **E** and **F**.



Scheme 3. Reaction of cyanoacetic acid. Reagents and conditions: **11** (1.0 mmol), sarcosine (1.5 mmol), $(CH_2O)_n$ (4.0 mmol of CH_2O), pyrrolidine (2.0 mmol), PhH, Δ, 3 h. Isolated yield based on **11** is depicted.

synthesis of 3-substituted *N*-methylpyrrolidines from monoalkyl malonates, cyanoacetic acids or 2-ketocarboxylic acids, sarcosine, and formaldehyde. These reactions proceed *via* a double decarboxylative domino-sequence mediated by pyrrolidine and involve β-amino acids and *N*-methylazomethine ylide as intermediates. The proposed approach is of great value owing to the operational convenience, broad substrate scope and the rapid construction of all three C–C and one C–N bonds of the pyrrolidine ring in one synthetic step promoted by a removable CO_2H group.

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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Double decarboxylative route to 3-substituted pyrrolidines: reaction of monoalkyl malonates and related carboxylic acids with sarcosine and formaldehyde

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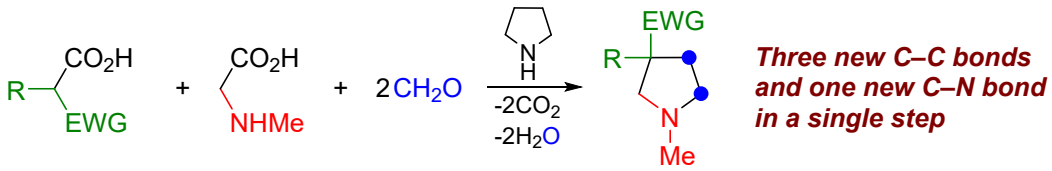

EWG = CO_2R, CN, ArCO, Ac; R = Alk, Ar, H 17–97% yield

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A rapid construction of pyrrolidine ring in a single synthetic step.

Formation of three C–C and one C–N bonds through a double decarboxylative reaction.