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One-Pot Three-Component Reaction for the Synthesis of α-(Aminoethyl)-α,β-enones

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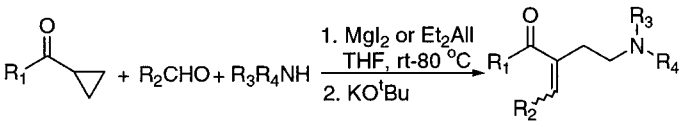
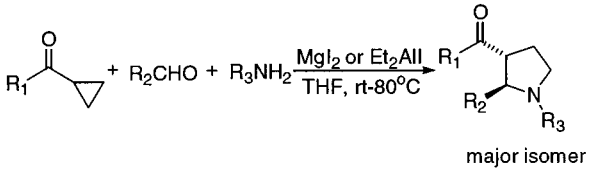
ABSTRACT



The synthesis of α-substituted α,β-enones by a new metal iodide-promoted one-pot three-component reaction involving commercially available cyclopropyl ketones, aldehydes, and secondary amines followed by base treatment is described.

Multicomponent reactions (MCRs) are an attractive concept for high-throughput chemistry that provides the ability to rapidly generate new complex products from simple substrates.[1] In the context of our chemical genomics initiative, taking advantage of the functional assay R-SAT™,[2] we recently reported a practical and efficient MCR[3a] by which substituted pyrrolidines were synthesized by reacting cyclopropyl ketones, aldehydes, and primary amines in the presence of MgI_2 or Et_2AlI (Scheme 1).

Scheme 1. Metal Iodide-Promoted Three-Component Reaction



A natural extension of that work was to explore the possibility of replacing the primary amines with secondary amines. Thus, initial assembly of a pyrrolidinium salt followed by a Hofmann elimination[4] would generate α-substituted α,β-enones (Scheme 2).

α,β-Enones represent a common feature in many useful reactions, e.g., Diels−Alder reactions,[5] Stetter reactions,[6] Michael additions,[7] Baylis−Hillman reactions,[8] Juliá−Colonna epoxidations,[9] and Robinson annulations.[10] Furthermore, in addition to possessing cytotoxic activities and anticancer properties (chalcones),[11] α,β-enones are frequently used as branching points for the creation of drug-like heterocyclic libraries (isoxazolines,[12] tetrahydropyrimidines,[12]

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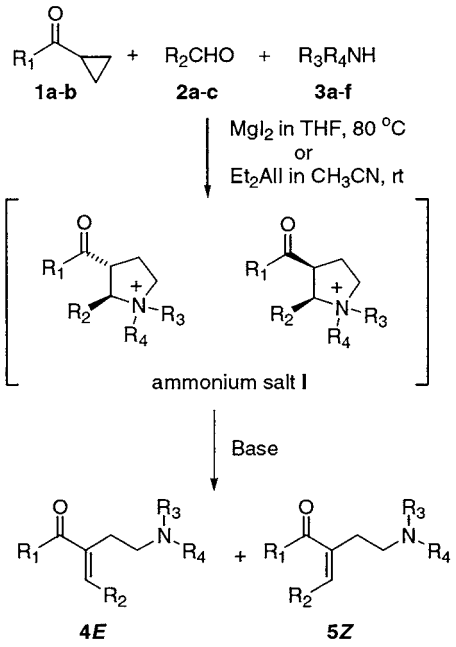
Scheme 2. Metal Iodide-Promoted Three-Component Reaction



dihydropyrimidiones,[13] pyrimidines,[13] pyridines,[13,14] benzothiazepines,[15] pyrazoles,[13] pyrazolones,[16] dihydropyran-2-ones,[17] and pyrazolines[18]). Consequently, numerous methods for the synthesis of α,β-enones have been reported,[19] including the frequently used Claisen−Schmidt condensation.[19b]

However, in terms of the ease of adapting reaction conditions and the availability of building blocks, few methods are available for parallel synthesis of α,β-enones.[13,20] We herein present an MCR that provides a more efficient and practical way to introduce additional diversity into the enones, thus resulting in α-substituted α,β-enones.

An investigation of the reaction conditions was conducted by using cyclopropyl phenyl ketone (**1a**), benzaldehyde, and piperidine (**3f**) as a representative combination set. Reactions promoted by MgI_2 or Et_2AlI were tested in different solvents (toluene, CH_2Cl_2, hexane, THF, and acetonitrile) and temperatures (rt, 50 °C, and at reflux). In general, THF and acetonitrile gave the most promising results for both MgI_2 and Et_2AlI, even though Et_2AlI worked in all tested solvents. Temperatures above 50 °C gave the best results in the MgI_2-promoted reactions, while room-temperature turned out to be most favorable for the Et_2AlI-promoted reactions. Further optimization revealed MgI_2 in THF at 80 °C and Et_2AlI in acetonitrile at ambient temperature to be the superior reaction conditions for the respective metal iodide. The LC/MS traces of the crude reactions showed only a single impurity. This peak was identified as the α,β-enone generated by premature Hofmann elimination from the ammonium salt. To force the elimination reaction to completion, addition of a base was necessary. Several bases were evaluated (KOH, Et_3N, NH_3, K_2CO_3, and KO^{t}Bu), and the non-nucleophilic KO^{t}Bu provided the best results.

The overall efficiency for the enone synthesis was evaluated by using this base under different conditions (Table 1).

Table 1. Metal Iodide-Promoted Three-Component Reaction Followed by Hofmann Elimination Using KO^{t}Bu[a]

entry	metal iodide	solvent	temperature (°C)[b]	yield of **4**/**5** (%)[c]
1	MgI_2	THF	80	57
2	MgI_2	CH_3CN	80	60
3	Et_2AlI	THF	rt	34
4	Et_2AlI	CH_3CN	rt	34
5	MgI_2	THF	80	10[d]

[a] Reactions were carried out in parallel (0.1 mmol scale) using **1a**, benzaldehyde, and **3f**. [b] Temperatures for the three-component reaction. Eliminations were performed at room temperature. [c] Overall isolated yields. After aqueous workup, purification was achieved by using PS-isocyanate scavenger resin followed by SCX IEC. [d] Base was added from the beginning in the three-component reaction.

Reactions were performed with the standard set of substrates (**1a**, benzaldehyde, and **3f**) at a 0.1 mmol scale. The final product was isolated in >95% purity by IEC regardless of the reaction yield. From these data, it was evident that MgI_2 was the reagent of choice, with yields around 60%, while the Et_2AlI-promoted reaction gave roughly 30% yield. Introducing the base from the start gave a much lower yield of the desired product (entry 5, Table 1).

Formation of the pyrrolidinium salt required approximately the same time as the pyrrolidine formation previously reported.[3a] After 7 h, the starting materials had been consumed, and an analysis of the crude product by LC/MS showed that a clean reaction had taken place. The subsequent elimination step was efficient, and after 1−2 h, the ammonium salt had been transformed to the final product.

The scope and limitation of the reaction was tested using various combinations of the starting materials shown in Figure 1, and the results from this collection of reactions are presented in Table 2.[21]

No significant patterns regarding yields and *E*/*Z* ratios were observed using the different combinations of aldehydes **2a**−

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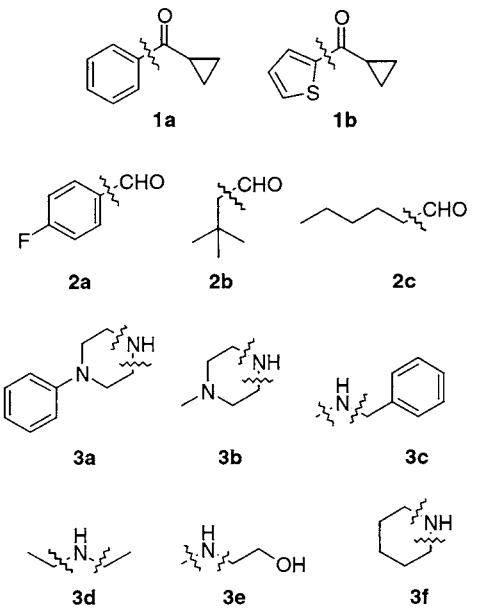


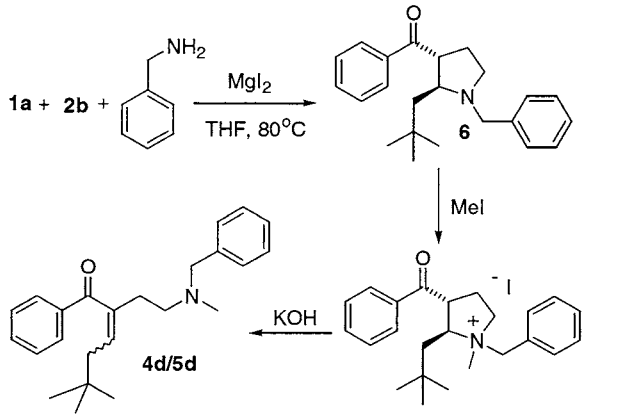
Figure 1. Starting materials used in the three-component reaction.

c, amines **3a**−**f**, and cyclopropyl ketones **1a**,**b**. Except for aldehyde **2c**, this MgI_2-promoted three-component reaction gave good yields that varied between 37 and 79%. Cyclic amines **3a** and **3b** gave slightly higher yields than acyclic **3c**−**e**, and changes in the aldehyde or cyclopropyl ketone had little or no effect on the yields. Not surprisingly, as was also seen in our previously reported three-component reaction, the major difference between using MgI_2 or Et_2AlI was in the use of the aliphatic aldehyde **2c**. MgI_2-promoted reaction resulted in a very low yield of **4j**/**5j**, while the Et_2-AlI-promoted reactions gave products in 66% yield. Additional functionality, a basic nitrogen or a hydroxyl group, present in the secondary amines **3b** and **3e**, respectively, were tolerated.

In general, to make the procedure efficient for library synthesis, all reagents and solvents were used as purchased and no special precautions such as predrying vials or performing the reaction under an inert atmosphere were used.

Since relatively few unsymmetrical secondary amines are commercially available, an alternative approach was investigated (Scheme 3). After an MgI_2-promoted three-component reaction using **1a**, **1b**, and benzylamine, generating the anti isomer exclusively, quaternization (MeI in CH_3CN, rt) followed by base treatment (KOH, rt) gave a 1:2 *E*/*Z* mixture of **4d**/**5d**. Using *N*-methylbenzylamine (**3c**) directly (entry 4, Table 2) gave a 2:1 ratio. The wealth of readily available primary amines and alkyl halides makes this route attractive when the corresponding secondary amines are not commercially available.

Scheme 3. MgI_2-Promoted Three-Component Reaction, Followed by Quaternization and Hofmann Elimination



The reason for the slightly different *E*/*Z* ratios of enones from the two methods is not apparent. A well-defined relative configuration did not improve the ratio in the final product.[22] Determination of whether the modest ratio is a result of racemization processes via enolate formation or a nonoptimal conformation for a Hofmann elimination (Scheme 4) resulting in an E1-like reaction requires further studies. As shown by the Newman projections, the disfavored conformations

Table 2. MgI_2 and Et_2AlI-promoted Three-component Reaction Followed by Treatment with K^{t}OBu[a]

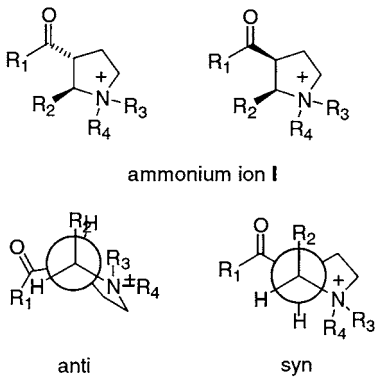
entry	cyclopropyl ketone	aldehyde	amine	product[d]	yield[e] (%)	dr[f,g] (*E*/*Z*)
1[b]	**1a**	**2a**	**3b**	**4a**/**5a**	72	4:1
2[b]	**1a**	**2b**	**3a**	**4b**/**5b**	65	1:1
3[b]	**1a**	**2b**	**3b**	**4c**/**5c**	66	1:1
4[b]	**1a**	**2b**	**3c**	**4d**/**5d**	52	2:1
5[b]	**1a**	**2a**	**3d**	**4e**/**5e**	56	6:1
6[b]	**1b**	**2a**	**3a**	**4f**/**5f**	79	3:1
7[b]	**1b**	**2b**	**3b**	**4g**/**5g**	69	1:1
8[b]	**1b**	**2b**	**3e**	**4h**/**5h**	37	4:1
9[c]	**1a**	**2a**	**3a**	**4i**/**5i**	58	6:1
10[c]	**1a**	**2c**	**3a**	**4j**/**5j**	66	1:1

[a] Reactions were performed according to the general procedure described in ref 21. [b] MgI_2 was used as the metal iodide. [c] Et_2AlI (1.5 equiv) was used as the metal iodide, and the reaction was performed at rt. [d] Mixture of diastereoisomers. [e] Isolated yields after flash chromatography purification. [f] Determined by LC/MS and ^1H NMR spectroscopy. [g] Stereochemistry of the major isomers **4a**, **4e**, **4h**, and **4i** was determined by NOESY experiments. Stereochemistry of the remaining compounds was tentatively assigned according to the general trend.

(21) **General Procedure for the MgI_2-Promoted One-Pot Three-Component Synthesis of α-Substituted α,β-Enones.** The aldehyde (1.0 mmol; 1.0 equiv), MgI_2 (1.0 mmol; 1.0 equiv), and cyclopropyl ketone (1.0 mmol; 1.0 equiv) were added sequentially to a solution of the amine (1.0 mmol; 1.0 equiv) in THF (4 mL) at rt, and the resulting mixture was shaken at 80 °C. After 7 h, the reaction was cooled to ambient temperature and KO^{t}Bu (1.5 mmol, 1.5 equiv) was added. After 2 h, the reaction was quenched with a saturated aqueous $Na_2S_2O_3$ solution (2 mL). The mixture was extracted with EtOAc (5 mL), and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL), dried over Na_2SO_4, filtered, and concentrated. The corresponding crude reaction mixture was purified by flash chromatography (CH_2Cl_2 + MeOH 4%) or by PS-isocyanate scavenger resin followed by an IEC, which afforded a mixture of pure products in reasonable yield.

(22) Using the secondary amine in the three-component reaction resulted in a 2,3-syn/-anti mixture of the corresponding ammonium salt indicated by LC/MS.

Scheme 4. Newman Projections of Intermediate Ammonium Salt I



would explain the lack of reactivity using the weaker base Et_3N at room temperature, a combination successfully used in similar elimination reactions (e.g., the REM strategy for the solid-phase synthesis of tertiary amines).[23] Relatively facile isomerization of the enones was also noticed. Upon storage for several days, the *E*/*Z* ratio of enone **4h**/**5h** changed from 4:1 to 10:1. However, this is of no great importance since the enone functionality is later used for the synthesis of aromatic heterocycles.

In summary, we have developed a new one-pot three-component reaction for the synthesis of α-aminoethyl-substituted α,β-enones from readily available cyclopropyl ketones, aldehydes, and secondary amines followed by Hofmann elimination. The yields in this metal iodide-promoted reaction are 37−79% with an *E*/*Z* ratio of 1:1 to 6:1. The protocol is readily adaptable for library synthesis, examples of which will be reported elsewhere.

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Supporting Information Available: General experimental procedures and compound characterization (^{1}H NMR, ^{13}C NMR, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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