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Synthesis of 1,2-disubstituted-3-alkylidenylpyrrolidines via a one-pot three-component reaction

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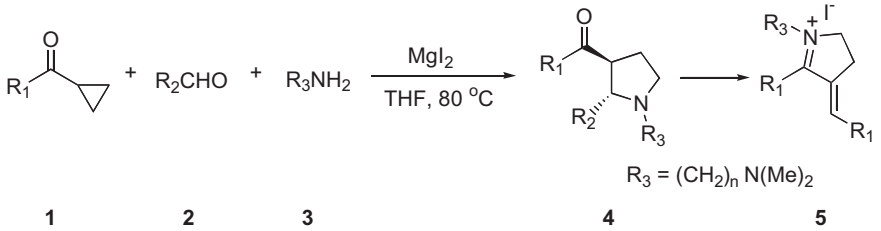
Abstract—Olsson's three-component reaction of cyclopropylketones, aldehydes, and primary amines was investigated for application to parallel synthesis. Using an excess of Et_2AlI at elevated temperatures, pyrrolidines **4**, the initial products reported by Olsson and co-workers, could be completely converted to pyrrolium salts **5**, by a reaction sequence involving a retro-aza-Michael addition followed by iminium salt formation. The pyrrolium salts **5** were then cleanly reduced in situ by $NaBH(OAc)_3$ to give 3-alkylidenylpyrrolidines **6**. In summary, this one-pot three-component reaction provided an efficient synthetic route to 3-alkylidenylpyrrolidines.

Multi-component reactions (MCRs) have proven to be an efficient methodology for the construction of novel, complex, and functionally dense molecules.[1] Recently, Olsson and co-workers[2] disclosed a new method for the synthesis of substituted pyrrolidine derivatives by a three-component reaction of cyclopropylketones, aldehydes, and primary amines. The chemistry was conducted by heating a mixture of the above three components in THF at 80 °C in the presence of a stoichiometric amount of MgI_2. Inspired by the efficiency of this method we began to study the potential application of the chemistry to the parallel synthesis of screening libraries. During the course of this effort, we had the opportunity to explore a diverse set of aldehydes and amines to better understand the scope of the reaction. To our surprise, the products, derived from amines with an additional basic site, underwent a decomposition to generate 1,2-disubstituted-3-alkylidenylpyrrolium salts **5** (Scheme 1). This intriguing observation prompted us to investigate the side reaction further with the goal of developing a facile synthesis of 3-alkylidenylpyrrolidines, a versatile class of heterocyclic intermediates that has been shown to provide access to a scaffold common to a variety of natural product.[3]

We selected eight primary amines containing additional functional groups to be reacted with cyclopropyl phenylketone and benzaldehyde to better understand



Scheme 1. Olsson's three-component reaction and the conversion of the initial products to pyrrolium salts.

Keywords: 3-Alkylidenylpyrrolidine; Multi-component reaction; Retro-aza-Michael addition; Pyrrolium salt.
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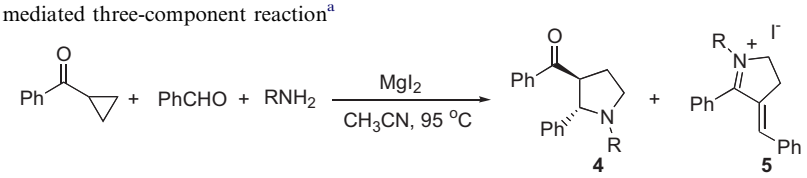
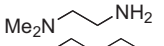
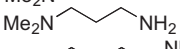
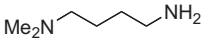
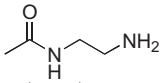
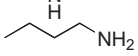
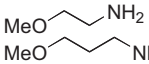
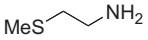
Table 1. Magnesium iodide mediated three-component reaction[a]



Entry	RNH_2	Ratio of 4/5[b]
1		1.0/5.2
2		0/1.0
3		0/1.0
4		0/1.0
5		1.0/trace
6		2.8/1.0
7		2.6/1.0
8		1.0/1.68

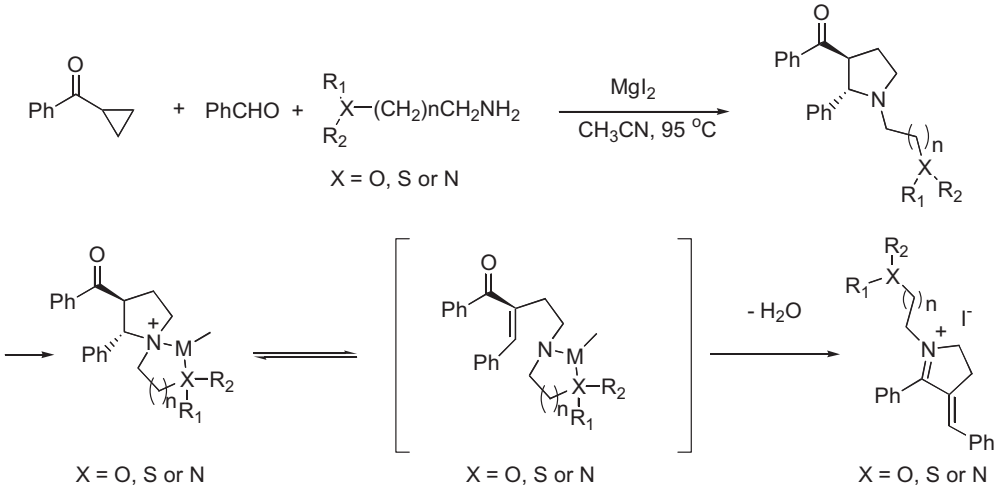
[a] Procedure and conditions: Benzaldehyde (0.4 M in CH_3CN, 750 μL, 0.3 mmol, 1.0 equiv), MgI_2 (250 mg, 0.9 mmol, 3.0 equiv), and cyclopropylphenylketone (0.4 M in CH_3CN, 750 μL, 0.3 mmol, 1.0 equiv) were added sequentially to a solution of amine (0.4 M, 750 μL, 0.3 mmol, 1.0 equiv) in acetonitrile at room temperature, and the resulting mixture was shaken at 95 °C for 20 h.

[b] The reaction mixture was analyzed by LC–MS and the product ratio was determined based on ELSD (evaporative light-scattering detection) response.

the role of the amine component, shown in Table 1. The product ratio of pyrrolidine **4** to pyrrolium salt **5** was determined by LC–MS analysis after 20 h at 95 °C. As expected from our initial results, amines containing a tertiary nitrogen atom or an amide group led to pyrrolium salts **5** as the major products or the only products (entries 1–4). However, the distance between the amino group and the second nitrogen moiety did not cause a pronounced effect on the ratio of products. In contrast, butyl amine produced only a trace of pyrrolium salt **5** with pyrrolidine **4** as the major product (entry 5), which was comparable to Olsson's results with pentyl amine. On the other hand, amines containing an ether group or a thio-ether group resulted in a mixture of both **4** and **5** (entries 6–8). These results suggested that the additional heteroatom enhanced the conversion of pyrrolidines **4** to pyrrolium salts **5**.

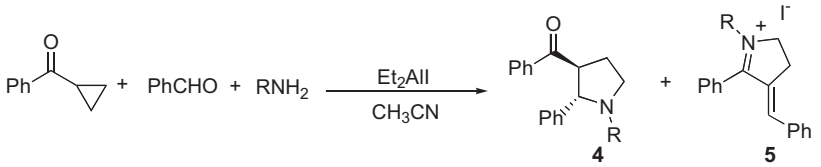
A mechanism was then postulated to explain these results, which begins with the conversion of the pyrrolidine **4** to an acyclic intermediate via a retro-aza-Michael addition reaction catalyzed by excess Lewis acid.[4] Co-ordination of Mg^{2+} with the pyrrolidine nitrogen would facilitate this key step while the presence of an additional heteroatom in the amine serves to enhance the chelation and further promotes the ring opening. This transient intermediate could then readily condense onto the carbonyl presumably catalyzed by the excess Lewis acid and driven by dehydration to give pyrrolium salt **5** (Scheme 2). Based on this proposed mechanism, we felt that the reaction scope could be expanded by using stronger Lewis acids.

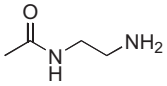
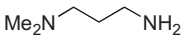
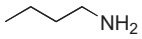
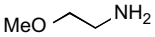
We tested Et_2AlI, a stronger Lewis acid that had already been successfully used in Olsson's report (Table 2). In



Scheme 2. A proposed mechanism for pyrrolium salt formation.

Table 2. Et_2AlI mediated pyrrolium formation[a]



Entry	RNH_2	Temperature (°C)	Ratio of 4/5[b]
1		70	0/1.0
2		70	0/1.0
3		95	0/1.0
4		80	0/1.0

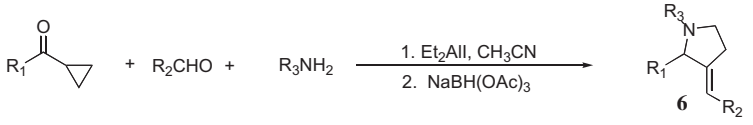
[a] Procedure and conditions: Benzaldehyde (0.4 M in CH_3CN, 750 μL, 0.3 mmol, 1.0 equiv), Et_2AlI (750 μL, 25 wt% solution in toluene, 0.75 mmol, 2.5 equiv), and cyclopropylphenylketone (0.4 M in CH_3CN, 750 μL, 0.3 mmol, 1.0 equiv) were added sequentially to a solution of amine (0.4 M, 750 μL, 0.3 mmol, 1.0 equiv) in acetonitrile at room temperature, and the resulting mixture was shaken for 20 h.

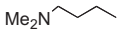
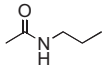
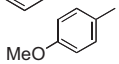
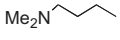
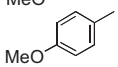
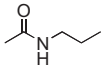
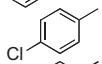
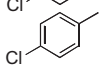
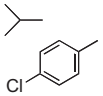
[b] The reaction mixture was analyzed by LC–MS and the product ratio was determined based on ELSD (evaporative light-scattering detection) response.

contrast to MgI_2, Et_2AlI accelerated the conversion of pyrrolidines **4** to pyrrolium salts **5** generated from amines with or without additional chelating groups (Table 2 entry 1–4). Additionally, the reactions with amines that did contain additional chelating groups could be driven to completion at a lower temperature (70 °C). Moreover, the conversion of butyl amine to the salt was quantitative at 95 °C. This suggested that the co-ordination between Et_2AlI and the pyrrolidine nitrogen was sufficient to initiate the retro-aza-Michael addition although the chelation from an additional heteroatom was still beneficial. Therefore, the optimized Et_2AlI-based conditions provided a more robust chemistry amenable to a diverse set of amines.

In order to further explore the utility of this conversion in the context of the three-component reaction, we applied the optimized Et_2AlI catalyzed reaction conditions to various combinations of cyclopropylketones, aldehydes, and amines, followed by in situ reduction[5] with $NaBH(OAc)_3$ to provide 1,2-disubstituted-3-alkylidenyl pyrrolidines **6**. It was noteworthy that only a single

Table 3. Pyrrolidines (**6**) synthesis via a three-component reaction followed by in situ reduction



Entry	Substrates			Reaction temperature for step 1 (°C)	Product	Yield[a] (%)
	R_1	R_2	R_3			
1				70	**6a**	62
2				70	**6b**	55
3				70	**6c**	69
4				70	**6d**	52
5				95	**6e**	71
6				95	**6f**	63
7				95	**6g**	55
8				95	**6h**	58
9				95	**6i**	75
10				95	**6j**	40

[a] Isolated yields and all compounds were characterized by ^1H NMR and ^{13}C NMR.

isomer of **6** was generated from the reactions as determined as *E* isomer by NOE analysis.[6] The overall reaction yields of the diverse set of substituted pyrrolidines **6** in Table 3 ranged from 40% to 75%, which demonstrates the generality and efficiency of this route. The ability to use readily available starting materials coupled with a convenient one-pot procedure[7] makes this chemistry a promising approach for the synthesis of pyrrolidine analogs.

In conclusion, a facile and efficient synthesis of pyrrolium salts **5** and alkylidenylpyrrolidines **6** has been achieved via the Et_2AlI promoted three-component reaction of cyclopropylketones, aldehydes, and amines at elevated temperatures. Further elaboration of both **5** and **6**, which are viewed as valuable synthetic intermediates, will be reported in due course.

Acknowledgements

We thank Ms. Jun Zhao for performing LC–MS analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.116. Experimental procedures, spectral data, and ^1H NMR spectra for compounds **6a–j** are available.

References and notes

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3. Some recent examples for preparing 3-alkylidenyl-pyrrolidine derivatives: (a) Molander, G. A.; Corrette, C. P. *J. Org. Chem.* **1999**, *64*, 9697–9703; (b) Zhou, Z. L.; Keana, J. F. W. *J. Org. Chem.* **1999**, *64*, 3763–3766; (c) Brown, R. C. D.; Fisher, M. *Chem. Commun.* **1999**, *16*, 1547–1548; (d) Pellegrini, N.; Schmitt, M.; Guery, S.; Bourguignon, J. *Tetrahedron Lett.* **2002**, *43*, 3243–3246.
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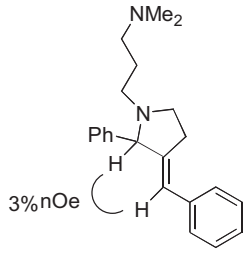
6. The stereochemistry was determined by NOE analysis.



7. General procedure: to a 7 mL vial, benzaldehyde (1.0 mL, 0.5 M solution in CH_3CN, 53.1 mg, 0.5 mmol, 1.0 equiv), Et_2AlI (1.0 mL, 25 wt% solution in toluene, 1.0 mmol, 2.0 equiv), and cyclopropylphenylketone (1.0 mL, 0.5 M solution in CH_3CN, 73.1 mg, 0.5 mmol, 1.0 equiv) were added sequentially to a solution of 3-(dimethylamino)propylamine (51.1 mg, 0.5 mmol, 1.0 equiv) in anhydrous acetonitrile (1 mL) at room temperature and the resulting mixture was shaken at 70 °C. After 20 h, the reaction was cooled to room temperature and $NaBH(OAc)_3$ (318 mg, 1.5 mmol, 3.0 equiv) was added to the reaction mixture. The vial was shaken for 6 h at room temperature. The reaction was then quenched with 1 mL of saturated $NaHCO_3$ and extracted with EtOAc (2×5 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction product was then purified by preparative thin-layer chromatography (10/1.5 chloroform/2.0 M ammonia in MeOH) to yield **6a** (99.3 mg, 62%) as thick oil. TLC (silica gel, 10/1 chloroform/2.0 M ammonia in MeOH, $R_f = 0.28$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.60–1.68 (m, 2H), 2.09–2.20 (m, 2H), 2.17 (s, 6H), 2.21–2.35 (m, 2H), 2.54–2.60 (m, 1H), 2.87–2.96 (m, 2H), 3.46 (t, $J = 7.8$ Hz, 1H), 3.83 (s, 1H), 5.75 (d, $J = 2.4$ Hz, 1H), 7.11–7.60 (m, 2H), 7.20–7.29 (m, 4H), 7.30–7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.4, 30.8, 45.4, 52.4, 52.8, 57.8, 75.9, 123.0, 126.1, 127.3, 127.9, 128.1, 128.2, 129.1, 137.9, 142.6, 147.3.