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Metal iodide mediated ring expansion of cyclopropanecarboxylic thioesters with imines

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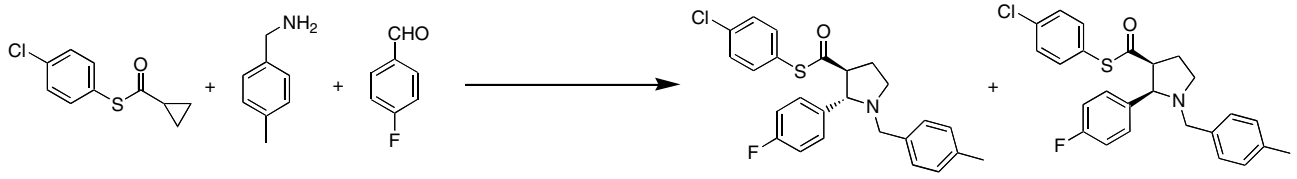
Abstract—Metal iodide mediated three-component reactions of cyclopropanecarboxylic thioesters **1**, aldehydes, and amines were developed. The initial products, pyrrolidines **2** were obtained in 39–73% yields, which could further be converted to lactams **4**, via sequential reactions of a retro-aza-Michael addition and an intramolecular cyclization. This methodology provided facile access to analogs of both pyrrolidines **2** and lactams **4**.

Metal iodide mediated ring expansion of activated cyclopropanes has recently attracted much attention because it provides an efficient method for the preparation of heterocyclic compounds.[1] Although many carbonyl groups have been used to activate cyclopropane, we are interested in thioesters recognizing that they can be easily prepared and the transformations of thioesters in organic synthesis are well documented.[2] In particular, direct amidation of thioesters and reductive alkylation of amines by thioesters under mild conditions allow further derivation of the products in a parallel fashion for compound library generation. Recently, Olsson and co-workers developed a convenient three-component reaction of cyclopropylketones, aldehydes, and amines for the synthesis of pyrrolidine derivatives.[1f] Since pyrrolidines are found in a variety of natural products and biologically active compounds, we envisioned that ring expansion of cyclopropanecarboxylic thioesters with imines would provide versatile synthetic intermediates not only for the construction

Table 1. Metal iodide mediated three-component reaction



1a **2a** **3a**

Entry	Metal iodide	Solvent	Temp (°C)	Time (h)	Ratio of **2a**/**3a**[a]	Yield[b] (%)
1	MgI_2 (2 equiv)	CH_3CN	85	20	0.9/1.0	59
2	Et_2AlI (2 equiv)	CH_2ClCH_2Cl	80	5	>99/1	57
3	Et_2AlI (1 equiv)	CH_2ClCH_2Cl	80	20		<5
4	ZnI_2 (2 equiv)	CH_3CN	85	20		0

[a] The ratios were determined by proton NMR of the crude reaction products.
[b] Isolated yield.

Keywords: Pyrrolidine; Three-component reaction; Thioester; Retro-aza-Michael addition.
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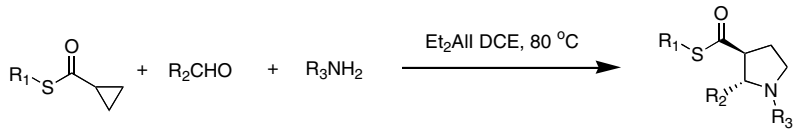
of β-proline combinatorial libraries, but also for the synthesis of some pyrrolidine alkaloids.

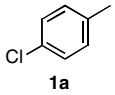
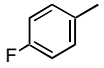
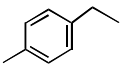
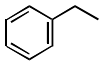
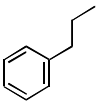
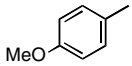
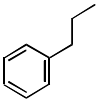
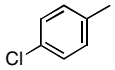
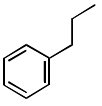
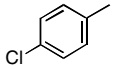
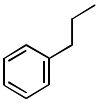
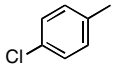
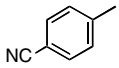
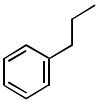
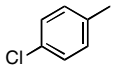
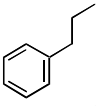
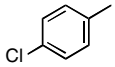
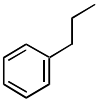
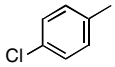
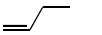
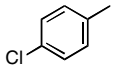
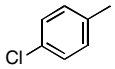
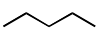
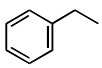
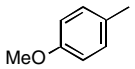
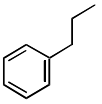
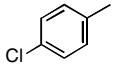
Our studies began with heating a mixture of thioester **1a**, 4-fluorobenzaldehyde, and 4-methylbenzylamine in the presence of 2 equiv of MgI_2 in acetonitrile at 85 °C. After 20 h, the reaction gave the desired pyrrolidines as a pair of isomers (**2a** and **3a**) in about a 1 to 1 ratio. When other metal iodides (ZnI_2 and Et_2AlI) were investigated, 2 equiv of Et_2AlI was found to push the reaction to completion in 5 h at 80 °C and gave **2a** as a predominate product in a 57% isolated yield,[3] as shown in Table 1.

To explore the scope of the reaction, the optimal Et_2AlI conditions were applied to various thioesters, aldehydes,

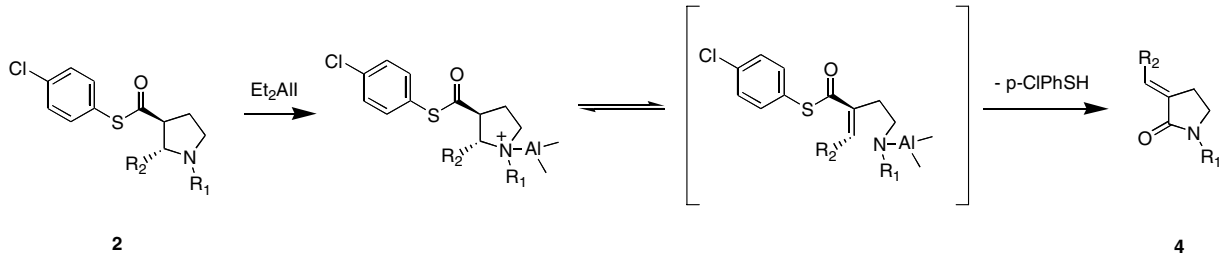
Table 2. Et_2AlI mediated three-component reaction[4]



1a-c **2a-j**

Entry	Substrates			Time (h)	Product	Yield (%)[a]
	R_1	R_2	R_3			
1	 **1a**			5	**2a**	57
2	 **1b**			5	**2b**	73
3	 **1c**			5	**2c**	59
4				5	**2d**	56
5				5	**2e**	61
6				5	**2f**	64
7				5	**2g**	49
8				5	**2h**	45
9				5	**2i**	43
10				5	**2j**	68
11				24	**2k**	39
12				5	**2l**	50

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



Scheme 1.

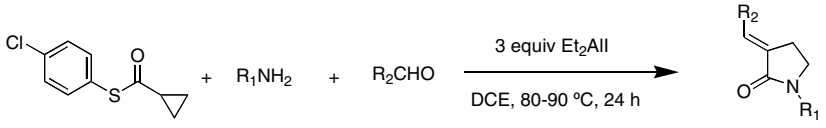
and amines as summarized in Table 2. Both aliphatic and aromatic thioesters worked under the set of conditions while aliphatic thioester **1c** gave a better yield in comparison with aromatic thioesters **1a** and **1b** (entries 2, 3, and 4). In addition, both aromatic and aliphatic aldehydes performed well in this reaction although electronic rich aldehydes, such as 4-methoxybenzaldehyde, reacted slowly and required a longer reaction time (entry 11). In all cases, the reaction gave one predominate isomer.

Along with pyrrolidines **2**, the reactions gave a small amount of lactams **4**. Further studies revealed that increasing either the amount of Et_2AlI used in the reaction or the reaction temperature increased the amount of lactams **4**. These side products came from the decomposition of pyrrolidines **2**, which was similar to the observation[5] we reported on the cyclopropylketone system. A mechanism was proposed in Scheme 1 to illustrate how pyrrolidines **2** were converted to lactams **4**. Acyclic intermediates generated from pyrrolidines **2** via a retro-aza-Michael addition reaction catalyzed by the Lewis acid underwent an intramolecular cyclization to give lactams **4**.

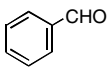
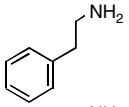
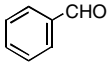
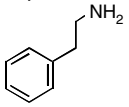
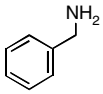
Recognizing that lactams **4** were important synthetic intermediates,[6] we focused our efforts on optimizing reaction conditions to generate lactams **4** exclusively. The three-component reaction was carried out using 3 equiv of Et_2AlI at 80 °C for 3 h followed by further heating the reaction mixture at 90 °C for 21 h. Under the new set of conditions, pyrrolidines **2**, the initial product of the reaction, were converted to lactams **4** completely in moderate to good yields, as shown in Table 3. It was noteworthy that only a single isomer of **4** was generated from the reactions as determined as *E* isomer by NOE analysis.[7]

In conclusion, a novel metal iodide mediated ring expansion of cyclopropanecarboxylic thioesters with imines was developed, by which pyrrolidines **2** or lactams **4** were prepared easily under two different sets of conditions by varying the amount of Et_2AlI, reaction temperature and time, starting from the same set of reagents.

Table 3. Lactam **4** formation[8]



1a **4a-d**

Entry	Substrates		Product	Yield (%)[a]	Mp (°C)
	R_1NH_2	R_2CHO			
1			**4a**	64	77–78
2			**4b**	71	134–135
3			**4c**	40	67–68
4			**4d**	42	64–65

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

The application of this methodology in the syntheses of β-proline libraries will be reported in due course.

Acknowledgments

We thank Dr. Feng Li for the NOE analysis.

References and notes

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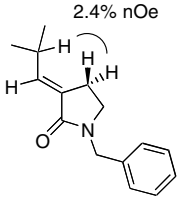
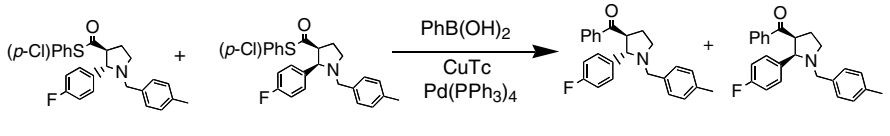
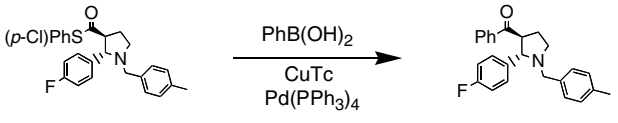
3. When MgI_2 was used to promote the reaction, **2a** and **3a** were formed as an inseparable mixture. These thioesters were converted to the phenylketones under Liebeskind's condition.[2a] When a mixture of **2a** and **3a** was used, the reaction gave phenylketones **5** and **6** as a pair of cis–trans isomers (Eq. 1). The proton NMR spectra of the phenylketones were compared with those of the authentic samples. Under the same condition, thioester **2a** gave phenylketone **5**, the trans isomer (Eq. 2). Based on these observations, **2a** was tentatively assigned as trans configuration.
4. General procedure: To a 7 mL vial, 4-fluorobenzaldehyde (62.1 mg, 0.5 mmol in 1.0 mL $ClCH_2CH_2Cl$, 1.0 equiv), Et_2AlI (1.0 mL, 25 wt % solution in toluene, 1.0 mmol, 2.0 equiv), and cyclopropanecarboxylic 4-chlorophenyl thioester (**1a**) (106.2 mg, 0.5 mmol in 1.0 mL $ClCH_2CH_2Cl$, 1.0 equiv) were added sequentially to a solution of 4-methyl benzylamine (60.6 mg, 0.5 mmol, 1.0 equiv) in anhydrous 1,2-dichloroethane (1 mL) at room temperature and the resulting mixture was shaken at 80 °C. After 5 h, the reaction was cooled to room temperature and then quenched with 2 mL of 0.5 M ethylenediaminetetraacetic acid disodium salt solution. The mixture was extracted with EtOAc (2 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction product was purified by preparative thin-layer chromatography (10% ethyl acetate in hexanes) to yield **2a** (124.8 mg, 57%) as a viscous oil. TLC (silica gel, 10% ethyl acetate in hexanes, $R_f = 0.42$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.09–2.15 (m, 1H), 2.21–2.29 (m, 1H), 2.33 (s, 3H), 2.38–2.43 (m, 1H), 3.04 (d, $J = 12.9$ Hz, 1H), 3.08–3.13 (m, 1H), 3.16–3.22 (m, 1H), 3.69 (d, $J = 8.2$ Hz, 1H), 3.73 (d, $J = 12.9$ Hz 1H), 7.06–7.14 (m, 6H), 7.26–7.28 (m, 2H), 7.36–7.38 (m, 2H), 7.46–7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 28.0, 52.3, 57.1, 61.1, 71.6, 115.5 ($J_{C-F} = 21.4$ Hz), 126.0, 128.5, 128.9, 129.3, 129.4, 135.6, 135.7, 135.8, 136.5, 136.8 ($J_{C-F} = 3.1$ Hz), 162.4 ($J_{C-F} = 245.7$ Hz), 198.4.
5. Huang, W.; O'Donnell, M.-M.; Bi, G.; Liu, J.; Yu, L.; Baldino, C. M.; Bell, A. S.; Underwood, T. J. *Tetrahedron Lett.* **2004**, *45*, 8511.
6. Some recent examples for preparing 3-alkylidenyl-pyrrolidin-2-one derivatives: (a) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, 4811; (b) Kitbunnadaj, R.; Zuiderveld, O. P.; De Esch, I. J. P.; Vollinga, R. C.; Bakker, R.; Lutz, M.; Spek, A. L.; Cavoy, E.; Deltent, M.-F.; Menge, W. M. P. B.; Timmerman, H.; Leurs, R. *J. Med. Chem.* **2003**, *46*, 5445; (c) Fielding, M. R.; Grigg, R.; Urch, C. J. *Chem. Commun.* **2000**, 2239.
7. The assignment of the stereochemistry was based upon an NOE analysis of lactam **4d**.



8. General procedure: To a 7 mL vial, benzaldehyde (53.1 mg, 0.5 mmol in 1.0 mL $ClCH_2CH_2Cl$, 1.0 equiv), Et_2AlI (1.5 mL, 25 wt % solution in toluene, 1.0 mmol, 3.0 equiv),



2a **3a** **5** **6** (1)



2a **5** (2)

and cyclopropanecarboxylic 4-chlorophenyl thioester (**1a**) (106.2 mg, 0.5 mmol in 1.0 mL $ClCH_2CH_2Cl$, 1.0 equiv) were added sequentially to a solution of butylamine (36.5 mg, 0.5 mmol, 1.0 equiv) in anhydrous 1,2-dichloroethane (1 mL) at room temperature and the resulting mixture was shaken first at 80 °C for 3 h, then at 90 °C

for 21 h. The reaction was cooled to room temperature and then quenched with 3 mL of 1.0 M NaOH aqueous solution. The mixture was extracted with EtOAc (2×10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction product was purified by preparative thin-layer chromatography (20% ethyl acetate in hexanes) to yield **4a** (73.3 mg, 64%) as a solid. TLC (silica gel, 20% ethyl acetate in hexanes, $R_f = 0.18$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, $J = 7.2$ Hz, 3H), 1.29–1.42 (m, 2H), 1.52–1.62 (m, 2H), 3.06 (dt, $J = 6.1$ Hz, 2.8 Hz, 2H), 3.41–3.51 (m, 4H), 7.26–7.50 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 20.1, 24.4, 29.4, 42.9, 44.5, 128.2, 128.6, 129.4, 129.7, 131.3, 136.0, 169.0.