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Application of the thioimidate cyclopropane rearrangement to heterocyclic synthesis. Preparation of diaryl pyrrolines

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Abstract—Substituent effects on the thioimidate cyclopropane rearrangement and factors affecting regioselectivity are reported. Palladium-mediated coupling of the pyrrolothiomethylimidate rearrangement products with Grignard reagents provides diaryl pyrrolines in good yields.

We recently disclosed the rearrangement of amino cyclopropyl thioamide **1** to pyrrolothiomethylimidate **2** and its subsequent conversion to 2,3-diamino pyrrolines **3** (Fig. 1).[1] We were interested in examining the effects of cyclopropane ring substitution on the rearrangement and in exploiting the utility of the resulting pyrrolothiomethylimidate intermediate(s) in transition metal-catalyzed cross-coupling reactions. Herein, we disclose our results in these two areas of inquiry.

To gauge the scope of the thioimidate cyclopropane rearrangement, a variety of substrates were prepared. Treatment of **4** with methyl iodide in acetone led to their facile thermal rearrangement to give pyrrolothiomethylimidates **6** via the intermediacy of thiomethylimidate **5** (Table 1).[2,3] Installation of electron donating or electron withdrawing groups demonstrated the generality of the thioimidate cyclopropane rearrangement. The nitrile (entry 8) was the only electron withdrawing group examined that adversely affected the course of the reaction. Entry 13, 1-methyl-2-phenylcyclopropane thioamide, demonstrates that the rearrangement proceeds efficiently in the case of a disubstituted cyclopropyl thioamide.[4,5]

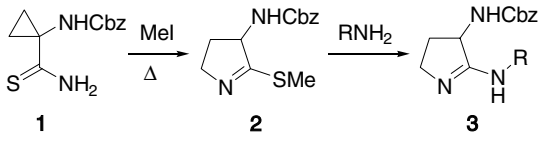

Figure 1. Synthetic route to 2,3-diamino pyrrolines.

The regioselectivity of the rearrangement is influenced by the nature of the group at the C-2 position (Table 1). A benzyl ester at C-2 (entry 10)[7] rearranges smoothly to give the 4-substituted product **6j**, but a phenyl group at C-2 leads to the 5-substituted product **6k** (entry 11).

The mechanism of the rearrangement likely involves acid catalyzed nucleophilic ring opening by the iodide counter ion.[1,8] According to Scheme 1, Path A (C-2 = CO_2Bn) depicts iodide attack at the less substituted center, leading to **6j**. When C-2 is phenyl (Path B), iodide addition occurs at the more hindered center, leading to the 5-substituted product **6k**.[6] The rationale behind this observed regioselectivity may involve stabilization of an incipient cation by phenyl group delocalization.

We investigated the propensity of select pyrrolothiomethylimidates to participate in C–C bond cross-coupling reactions. The possibility of using pyrrolothiomethylimidates as coupling partners with organometallic reagents was supported by the elegant work of Liebeskind[9] and Jacobi.[10] Although substituted pyrrolines have been reported in the literature, a paucity of methods exist for the synthesis of 2,3-[11–13] and 2,5-diaryl pyrrolines.[14–16] Similarly, few examples of cross-coupling reactions between cyclic thioiminoethers and organometallic reagents have been reported.[10]

Keywords: Cyclopropane rearrangement; Cross-coupling.
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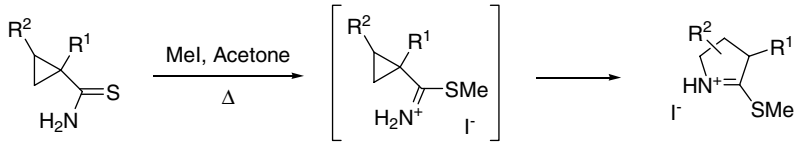
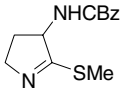
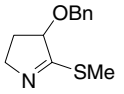
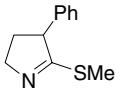
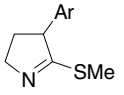
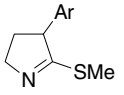
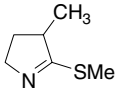
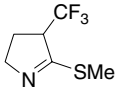
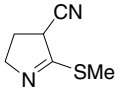
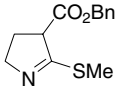
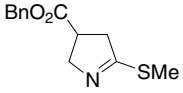
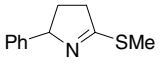
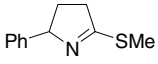
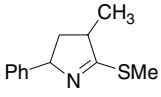
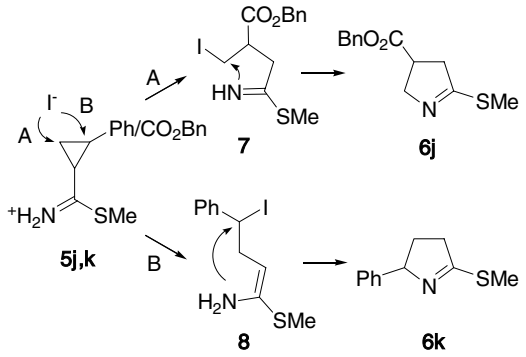
Table 1. One-pot thioimidate formation and subsequent thermal rearrangement to pyrrolothiomethylimidates



4 **5** **6a-m**

Entry	R^1	R^2	Temp (°C)	Time (h)	Pyrrolothiomethylimidate		Yield (%)[a]
1	NHCBz	H	60	2		**6a**	100
2	BnO	H	60	1.5		**6b**	95
3	Phenyl	H	45	3		**6c**	100
4	4-MeO Phenyl	H	45	5		**6d**	96
5	4-Cl Phenyl	H	45	1		**6e**	99
6	Methyl	H	60	1		**6f**	94
7	CF_3	H	60	4		**6g**	90
8	CN	H	60	5.5		**6h**	0[b]
9	CO_2Bn	H	60	2		**6i**	94
10	H	CO_2Bn	60	1.3		**6j**	99[c]
11	H	Phenyl	60	3		**6k**	95[c]
12	H	Phenyl	60	1		**6l**	99[d]
13	Methyl	Phenyl	60	1		**6m**	83[e]

[a] All yields given are for isolated products with purity >95% by ^{1}H NMR and LC/MS.
[b] Formation of thioimidate cyclopropane was characterized by ^{1}H NMR. Further heating induced its decomposition.
[c] Trans racemic isomer.
[d] The starting material was the (+)-*trans* cyclopropane enantiomer. The product obtained was a 55:45 mixture of enantiomers (Chiralcel OJ column).[6]
[e] Product was a mixture of cis and trans isomers.



Scheme 1. Regioselectivity of the rearrangement of **5j**,**k**.

Table 2 summarizes the palladium-catalyzed[17] cross-coupling reactions of pyrrolothiomethylimidates with organozinc or organomagnesium reagents.[18] Reaction with phenylmagnesium bromide provided higher yields (54–86%) of desired 2,3-diaryl pyrrolines.[19–21] Exclusion of palladium catalyst from the reaction (entry 6) resulted in no product formation.[22] But, the subsequent addition of catalyst drove the reaction to near completion, indicating the coupling reaction is not a simple addition–elimination process.[23] This methodology was also extended to the synthesis of 2,5-diaryl (entry 9) and trisubstituted pyrrolines (entry 10). Non-aryl pyrrolothiomethylimidates also participate in the cross-coupling reaction with Grignard reagents (entries 11 and 12).

In summary, we have extended the scope of the thioimidate cyclopropane rearrangement by employing a variety of substituted cyclopropyl thioamides. Further, we have demonstrated the versatility of the resulting pyrrolothiomethylimidates by subjecting them to palladium-catalyzed cross-coupling reactions with Grignard reagents to afford 2,3- and 2,5-disubstituted pyrrolines.

Acknowledgments

The authors thank Dr. John H. Hutchinson for initially suggesting the cross-coupling approach. We are grateful to Drs. Steven M. Pitzenberger and Sandor L. Varga for NMR analyses and to Mr. Carl F. Homnick for chiral chromatographic studies. We thank Dr. Mark G. Bock for helpful discussions.

References and notes

1. Kuduk, S. D.; Ng, C.; Chang, R. K.; Bock, M. G. *Tetrahedron Lett.* **2003**, 1437–1440.
2. Thioamides were synthesized as in Ref. 1.
3. Typical procedure for the synthesis of pyrrolothiomethylimidates: To a solution of 1-phenylcyclopropanecarbothioamide (4.1 g, 22.9 mmol) in dry acetone (150 mL) was added methyl iodide (4.9 g, 34.4 mmol) under nitrogen, and the reaction mixture was heated to 45 °C. After 1.5 h, a precipitate (pyrrolothiomethylimidate hydro iodide salt) was observed, and the reaction was heated for another 1.5 h. The reaction solution was concentrated in vacuo to afford 5-(methylthio)-4-phenyl-3,4-dihydro-2*H*-pyrrolium iodide (7.3 g, 100%). MS: (ES+) of 192.3 for $M+H^+$; ^1H NMR (500 MHz, $CDCl_3$): 7.46–7.41 (m, 3H), 7.25 (m, 2H), 4.51 (t, $J = 9.2$ Hz, 1H), 4.44 (m, 1H), 4.27 (m, 1H), 3.06 (s, 3H), 2.90 (m, 1H), 2.47 (m, 1H).
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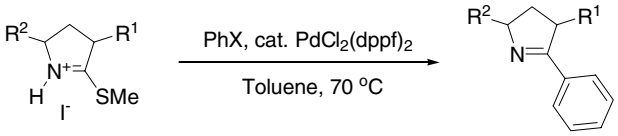
5. The disubstituted cyclopropyl thioamide **5m** was prepared as in Ref. 1 and by use of a modification of the method described in Ref. 4.
6. Table 1, entry 12 details the rearrangement of optically pure (+)-*trans*-2-phenylcyclopropanecarbothioamide. The product was a mixture of 5-phenylpyrrolothiomethylimidate enantiomers. The scrambling of the benzylic center may arise because of the cationic nature of the ion pairs or double inversion via a second equivalent of iodide.

Table 2. Pd-catalyzed cross-coupling reactions of pyrrolothiomethylimidates with organometallic reagents

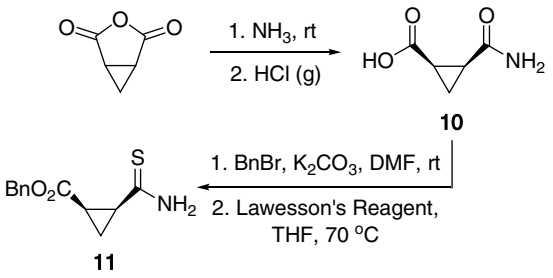


6b-e,g,k,m **9a-g**

Entry	Pyrrolothiomethylimidate	R^1	R^2	PhX (equiv)	Time (h)	Product	Yield (%)[a]
1	**6c**	Phenyl	H	ZnI (3)	1	**9a**	43[b]
2	**6d**	4-MeO Phenyl	H	ZnI (2)	1.5	**9b**	38[b]
3	**6e**	4-Cl Phenyl	H	ZnI (2)	1	**9c**	32[b]
4	**6k**	H	Phenyl	ZnI (4)	2	**9d**	37
5	**6c**	Phenyl	H	MgBr (2)	1.5	**9a**	86
6	**6c**	Phenyl	H	MgBr (6)	6	**9a**	58[c]
7	**6d**	4-MeO Phenyl	H	MgBr (3)	1.5	**9b**	78
8	**6e**	4-Cl Phenyl	H	MgBr (3)	1.5	**9c**	54
9	**6k**	H	Phenyl	MgBr (4)	2.5	**9d**	61
10	**6m**	Methyl	Phenyl	MgBr (7)	5.5	**9e**	53[d]
11	**6g**	CF_3	H	MgBr (3)	1	**9f**	25
12	**6b**	BnO	H	MgBr (5)	1	**9g**	46

[a] All yields given are for isolated products with purity >95% by ^1H NMR and LC/MS.
[b] $PdCl_2(Ph_3P)_2$ was used as the catalyst.
[c] Initially, the reaction was devoid of catalyst. Upon the addition of 10 mol % $PdCl_2(dppf)_2$, the reaction was judged >90% complete by LC/MS.
[d] The yields correspond to the isolated cis (37%) and trans (16%) isomers as determined by NMR studies.

7. Nucleophilic addition of ammonia to the commercially available 3-oxabicyclo[3.1.0]hexane-2,4-dione gave the desired *cis*-aminocarbonylcyclopropane carboxylic acid **10**. Benzylation and subsequent treatment with Lawesson's reagent provided the desired thioamide **11**.



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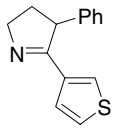
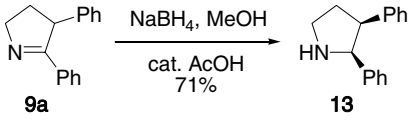
17. We utilized 1,1-bis(diphenylphosphinoferrocene) palladium (II) dichloride as the favored catalyst over dichloro bis(triphenylphosphine) palladium (II). Although the latter gave slightly higher yields, triphenylphosphine oxide generated from the reaction may be difficult to separate from the desired product.
18. We initially attempted a copper (I) thiophene-2-carboxylate mediated palladium-catalyzed cross-coupling with boronic acids as described by Liebeskind.[9b,c] However, the reaction did not proceed in greater than 25% completion and the product was difficult to isolate.
19. Typical procedure for the synthesis of disubstituted pyrrolines: A solution of 5-(methylthio)-4-phenyl-3,4-dihydro-2*H*-pyrrolium iodide (0.306 g, 0.96 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloro-palladium(II), complex with DCM (1:1) (0.0702 g, 0.10 mmol) and toluene (10 mL) was heated to 70 °C under nitrogen, and reaction mixture was treated with 1 M solution of phenylmagnesium bromide in THF (1.92 mL, 1.9 mmol). After heating for 1.5 h, the reaction was diluted with EtOAc and washed with a saturated solution of ammonium chloride. The organic layer was separated from the aqueous layer, dried over sodium sulfate, filtered and concentrated to an orange oil. The crude residue was subjected to silica gel chromatography eluting with 0–15% EtOAc in hexanes to afford 4,5-diphenyl-3,4-dihydro-2*H*-pyrrole (0.183 g, 86%). MS: (ES+) of 222.3 for $M+H^+$; ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, $J = 7.1$ Hz, 2H), 7.32–7.25 (m, 5H), 7.17 (t, $J = 7.3$ Hz, 1H), 7.12 (d, $J = 7.3$ Hz, 2H), 4.50 (d, $J = 7.8$ Hz, 1H), 4.13 (m, 2H), 2.58 (m, 1H), 1.99 (m, 1H).
20. Further investigations into the scope of the organomagnesium reagent with aliphatic and vinyl Grignard reagents failed to produce desired product. Yet, the use of an alternate aryl Grignard reagent such as 3-thienylmagnesium iodide provided the diaryl pyrroline **12** in 51% yield.



12

21. *cis*-2,3-Diaryl pyrrolidines are readily accessible via sodium borohydride reduction of 2,3-diaryl pyrrolines.[13] The relative stereochemistry of 2,3-diphenyl pyrrolidine **13** was determined by NMR studies.



9a **13**

22. There are examples of uncatalyzed addition of Grignard reagents to thioethers in the literature, but the yields (26–32%) are generally low, see: Gessner, W.; Takahashi, K.; Brossi, A. *Helv. Chim. Acta* **1987**, *70*, 2003–2010.
23. A similar reaction was performed with phenyl lithium in a non-catalytic system to scope the reactivity of the pyrrolothiomethylimidates. We obtained the desired 2,3-diphenyl pyrroline in only 16% yield, but also saw double addition of phenyl lithium by LC/MS and crude ^1H NMR, which was not isolated.