Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1437–1440

TETRAHEDRON LETTERS

Synthesis of 2,3-diaminodihydropyrroles via thioimidate cyclopropane rearrangement

Scott D. Kuduk,* Christina Ng, Ronald K. Chang and Mark G. Bock

Department of Medicinal Chemistry, Merck Research Laboratories, WP14-3, Sumneytown Pike, PO Box 4, West Point, PA 19486, USA

Received 4 December 2002; accepted 17 December 2002

Abstract—The synthesis of novel 2,3-diaminodihydropyrroles is reported. The key step is a thiomethylimidate cyclopropane rearrangement to afford a pyrrolothiomethylimidate intermediate. Reaction of this intermediate with amines produced the title compounds in good yields. The scope and mechanism of the reaction is discussed. © 2003 Published by Elsevier Science Ltd.

The thermally induced rearrangement of substituted cyclopropanes to 2-pyrrolines was first reported by Cloke in 1929 (Fig. 1).[1] This was followed by Stevens who applied the reaction as a general method toward the synthesis of pyrrolidine (or pyrroline) containing alkaloids.[2] Stevens further showed that the rearrangement is not purely a thermal process and that an acid catalyst is required. This cyclopropyl iminium ion rearrangement has been applied in the synthesis of a number of pyrrolidine containing alkaloids. The scope, mechanism, and applications toward alkaloid synthesis have been reviewed.[3]

In connection with a synthesis program, we required ready access to substituted 2,3-diaminodihydropyrroles. Surprisingly, we were unable to find examples of this core structure in the literature. We were intrigued by the possibility of using an imidate variant of the cyclopropyl iminium ion reaction to access pyrroloimidate products which would be useful intermediates for reaction with amines to afford the desired 2,3-diaminodihydropyrroles (Fig. 2).

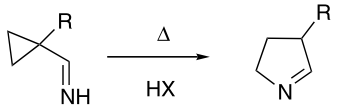


Figure 1. The cyclopropyl iminium ion rearrangement.

It was envisioned that formation of the imidate would be straightforward via methylation of the corresponding thioamide. Thus, according to Scheme 1, commercially available Cbz protected 1-aminocyclopropane-1-carboxylic acid was converted to the amide and subsequent treatment with Lawesson's reagent cleanly afforded the thioamide **1** in 85% yield. Attempted imidate formation was carried out with excess methyl iodide in acetone at temperatures ranging from ambient temperature to 60°C.[4] The reaction required 60°C for complete conversion, and we were pleased to see that the ^{1}H NMR spectrum of the crude reaction mixture showed the formation of rearrangement product **3** in essentially quantitative yield.[5] The intermediate imidate **2** was not observed and, therefore, must rapidly rearrange under the reaction conditions which were employed. To the best of our knowledge, this is the first example of a cyclopropyl thioimidate rearrangement.

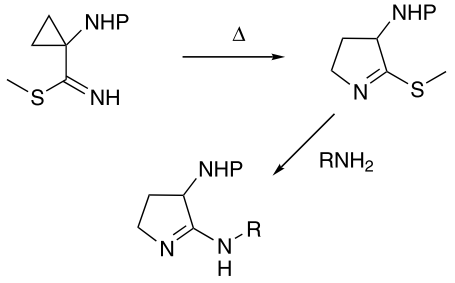
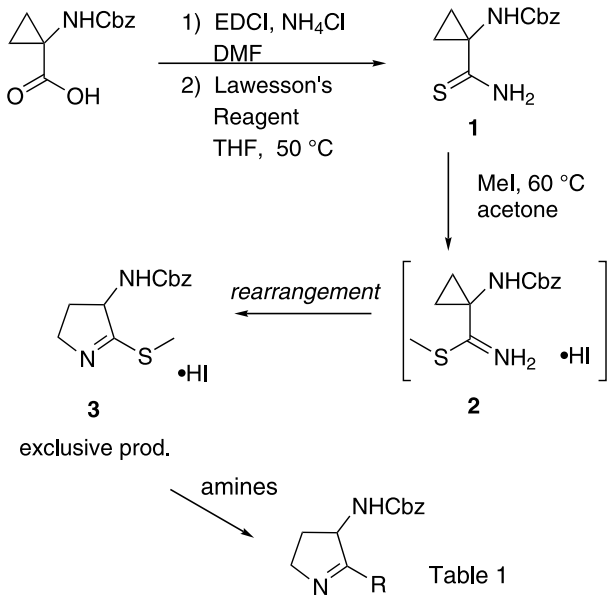


Figure 2. Proposed route to 2,3-diaminodihydropyrroles.

Keywords: cyclopropane; rearrangement; dihydropyrroles; imidate.

* Corresponding author. Tel.: 1-215-652-5147; fax: 1-215-652-3971; e-mail: scott_d_kuduk@merck.com

0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
PII: S0040-4039(02)02847-2



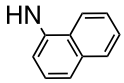
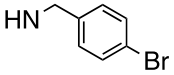
Scheme 1. Imidate formation and rearrangement.

The pyrrolothioimidate **3** then served as a useful intermediate for subsequent reaction with amines to afford the desired 2,3-diaminodihydropyrroles. We surveyed several amines to explore the reactivity of **3**. Results are summarized in Table 1.[6] The product yields are unoptimized for the three-step process of imidate formation, rearrangement, and amine displacement.

As can be seen in Table 1, most amines examined react efficiently with the pyrroloimidate **3**. Ammonia and other simple primary amines, such as isopropylamine, afford product at 50°C in THF. Smooth reaction occurred at room temperature when the more nucleophilic *O*-benzylhydroxylamine was employed to provide a 73% yield of product. Consistent with their increased steric demand, secondary amines were less reactive. Diethylamine in THF yielded no reaction product and required DMSO and higher temperature to effect reaction. Nevertheless, only a modest 30% yield (at 50% conversion) was obtained after 48 h at 120°C. In contrast, constraining the ethyl groups in the form of a piperidine allows for a smooth reaction in THF at 50°C.

The displacement reaction of **3** with weakly nucleophilic amines was also examined (examples 6 and 7). Of note was the reaction with aromatic amines. While aniline afforded a 72% yield of product in DMF at 60°C, the more sterically encumbered α-naphthylamine proved problematic. It required DMSO and 120°C to effect reaction, but led to low yield and extensive by-product formation.

Table 1. Reaction of pyrrolothioimidate with amines

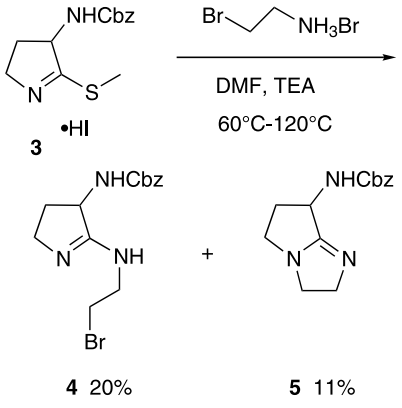
Entry	Amine	Solvent	Temp	Time (h)	R	Yield[a]
1	NH_3	THF	50	2	NH_2	49
2	$iPrNH_2$	THF	50	2	NHiPr	56
3	$BnONH_2$	THF	RT	0.5	NHOBn	73
4	Et_2NH	DMSO	120	48	NEt_2	30
5	piperidine	THF	50	2		69
6	aniline	DMF	60	2	NHPh	72
7	α-naphthylamine	DMSO	120	48		5
8	$BrBnNH_2$	THF	50	2		65

[a]All yields given are for isolated products with purity >95% by ^1H NMR and LC/MS

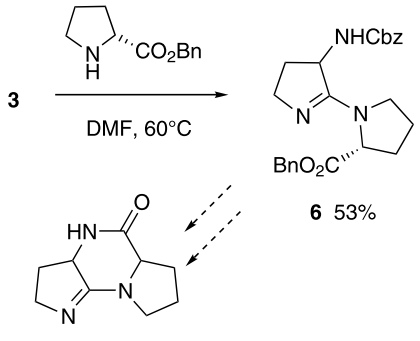
Having investigated the reactivity of thioimidate **3** with amines, we sought to apply this reaction to the preparation of pharmacologically relevant templates. One such example is the reaction between thioimidate **3** and 2-bromoethylamine (Scheme 2). The reaction was carried out first at 60°C in DMF to effect displacement of the thiomethyl group by the amine component to afford **4**. Heating to 120°C overnight resulted in subsequent alkylation of the nitrogen to afford a mixture of **4** and desired product **5**. The latter compound represents an amine-substituted variant of a class of indolamine *N*-methyl transferase inhibitors.[7]

In another example, the reaction of **3** with benzyl protected L-proline was examined (Scheme 3). The yield was a modest 53% due to the steric hindrance afforded by the ester, but the product **6** has considerable potential for further chemical elaboration. Although the reaction conditions of the previous two examples require optimization, they do point out the method's utility for making useful structural templates.

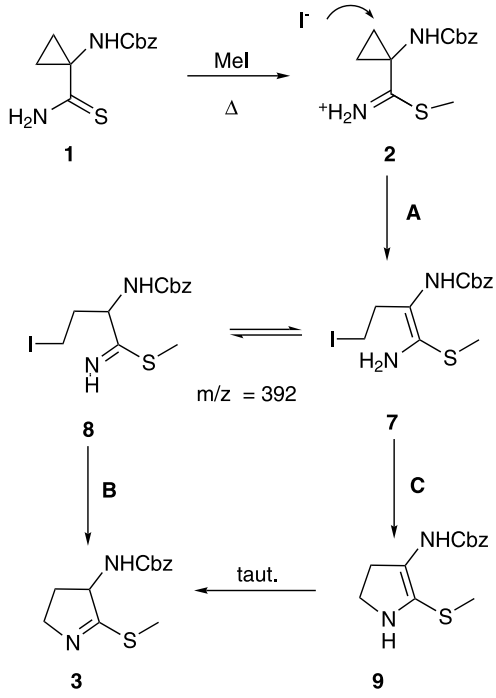
The definitive mechanism of the cyclopropyliminium ion rearrangement has not been established, but several empirical observations have led to proposals for possible reaction pathways.[3] The proposed mechanism for the thioimidate version of this reaction follows a similar path to the classical rearrangement. In the system described in Scheme 4, the initial step is formation of the imidate in acetone with methyl iodide at 60°C. Intermediate **2** was not observed and likely rearranges



Scheme 2.



Scheme 3.



Scheme 4. Proposed mechanism.

rapidly at the temperature required for imidate formation. The classical cyclopropyliminium ion rearrangement usually requires temperatures of 100–140°C for rearrangement to occur, although examples of *N*,*N*-dialkyl or *N*,*N*-alkyl-acyl transformations occur at lower temperatures.[8] The thioimidate may have enhanced nucleophilicity and allows the reaction to proceed at a lower temperature.

The key to the proposed mechanism is the absolute requirement of HX to catalyze the reaction. The protonation of the thioimidate is required to activate the system. In the event, the nucleophilic counter ion effects the ring opening of **2** to afford enamine **7** (step A). In the second step (B), **7** tautomerizes to the imine **8**, which cyclizes to the desired rearrangement product **3**. Alternatively, **7** could undergo intramolecular alkylation, followed by tautomerization to the desired imidate (path C). Although intermediates **7** and **8** were not isolable, it was possible to detect a mass ion of m/z 392 via LC/MS corresponding to the presence of either **7** or **8**. The observation of this intermediate with a mass ion of 392 lends support to the two step process of acid catalyzed nucleophilic ring opening[9] followed by cyclization as compared to an alternative mechanism proposed by Wasserman.[10]

In summary, the first example of a cyclopropyl thioimidate rearrangement has been reported. The resulting pyrrolothioimidate products have been shown to undergo displacement with amines to afford Cbz protected 2,3-diaminodihydropyrroles in fair to good yields for the three step process. The rearrangement of cyclopropanes with other substituents and other synthetic applications of the pyrrolothioimidates will be reported in due course.

Acknowledgements

The authors would like to thank Dr. Mike Wood for helpful discussions.

References

1. Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174.
2. Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193–198.
3. Boeckman, R. K.; Walter, M. A. *Advances in Heterocyclic Natural Product Synthesis*; JAI Press: New York, 1990; Vol. 1, pp. 1–40.
4. *Typical procedure for the imidate formation and rearrangement*: To a stirred solution of benzyl 1-(aminocarbonothioyl)cyclopropylcarbamate **1** (1.60 g, 6.83 mmol) in 60 mL of acetone was added methyl iodide (1.70 mL, 27.3 mmol). Additional methyl iodide was added to the reaction as needed. The mixture was refluxed under N_2 for 2 h and concentrated in vacuo to obtain a yellow foam **3** that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 265.2 for $M+H^+$: ^1H NMR (300 MHz, MeOH-d_4): δ 7.33 (bm, 5H), 5.34 (d, $J=6.5$ Hz, 2H), 5.13 (s, 2H), 3.93–4.16 (m, 2H), 2.73 (s, 3H), 2.69 (m, 1H), 2.39 (m, 1H).
5. We have also carried out the reaction with Boc protection as a complement to the Cbz examples shown. While the rearrangement occurred under identical conditions, the amine addition products were more difficult to isolate and purify.
6. *Typical procedure for the formation of diaminodihydropyrrolidines*: To a solution of the crude rearrangement product HI salt **3** (0.10 g, 0.255 mmol) in 1 mL of THF was added piperidine (0.66 g, 0.77 mmol), and the mixture was heated to 50°C for 2 h. The mixture was concentrated in vacuo and purified by HPLC to afford the product (Table 1, entry 5) TFA salt (71 mg, 69%) as a white foam that gave a proton NMR spectrum consistent with theory and a mass ion (ES+) of 302.1 for $M+H^+$: ^1H NMR (300 MHz, MeOH-d_4): δ 7.34 (bm, 5H), 5.22 (bt, $J=5.4$ Hz, 1H), 5.12 (m, 1H), 3.85 (m, 1H), 3.66 (m, 2H), 3.39 (m, 1H), 2.62 (m, 1H), 2.13 (m, 1H), 1.37–1.71 (m, 6H).
7. Rokach, J.; Hamel, P.; Hunter, N. R.; Reader, G.; Rooney, C. S.; Anderson, P. S.; Cragoe, E. J.; Mandel, L. R. *J. Med. Chem.* **1979**, *22*, 237–244.
8. (a) Boeckman, R. K.; Jackson, P. F.; Sabatucci, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 2191; (b) Boeckman, R. K.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *100*, 8250.
9. Additional support for this mechanism was gained by using dimethyl sulfate in place of methyl iodide in the reaction with thioamide **1**. In this case we only observed the unrearranged product **2**, and not **3**, consistent with the poor nucleophilicity of the sulfate counterion. We have also prepared the *O*-methylimidate of benzyl 1-(aminocarbonyl)cyclopropylcarbamate using trimethyloxonium tetrafluoroborate. All attempts to rearrange this material were unsuccessful. We believe the failure of this imidate to undergo rearrangement is because the resulting HBF_4 salt is not conducive for nucleophilic ring opening. Similar observations have been noted in the classical cyclopropyliminium ion rearrangement (Ref. 3). Interestingly, addition of halide salts to the tetrafluoroborates did not result in rearrangement of the *O*-methyl imidates. We are continuing to investigate *O*-methyl imidates as substrates for this rearrangement.
10. Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1983**, *24*, 3409–3412.