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INTRAMOLECULAR THIOAMIDE PARTICIPATION REACTIONS

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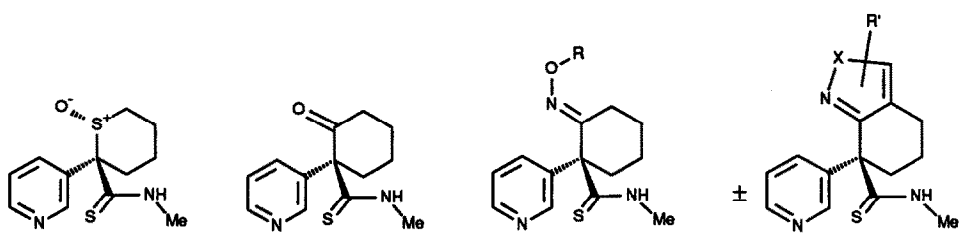
Abstract: *The intramolecular participation of the thioamide group during the attempted formation of* **10** *and* **13** *from* **8**, *led to the stereospecific formation of the versatile bicyclic intermediates* **9** *and* **14**, *respectively. Their use as valuable precursors to tetrahydroisoindazoles of type* **3** *(X = N) is demonstrated.*

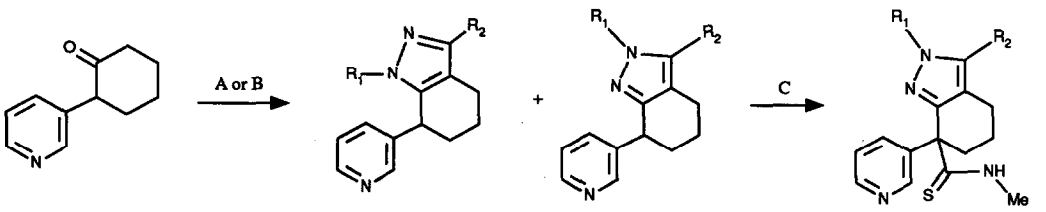
Compounds acting as potassium channel openers have therapeutic potential in a number of disease states such as hypertension and asthma.[1] Aprikalim (RP 52891, Scheme 1) is currently undergoing clinical evaluation for the treatment of cardiovascular disorders and, more recently, we have described the synthesis of the related (S)-ketone thioamide, **1**, which exhibited good *in vitro* potassium channel opening activity (IC_{90}= 0.4 μM).[2,3]



Scheme 1

As part of our programme to discover therapeutically useful potassium channel openers, we found that oxime derivatives of the type **2** were, in general, much more potent than **1** *in vitro*, although their enhanced intrinsic activity was not reflected *in vivo*, possibly due to rapid metabolism and poor absorption. Therefore, we decided to evaluate novel heterocyclic derivatives of the type **3** as metabolically stable, rigid replacements of the oxime functionality. Our preliminary study was concerned with tetrahydroisoindazoles of type **3** (X = N) and we report herein two expedient approaches to this class of heterocyclic compound which should also allow access to the pure (S)-enantiomers.

The versatile intermediate, 2-(3-pyridyl)cyclohexanone,[2,3] **4**, was converted by two different procedures (A and B), to a mixture of the substituted tetrahydroisoindazole isomers of type **5** and **6** (Scheme 2). After separation of the regioisomers, both **6a** and **6b** were acylated with methyl isothiocyanate to afford the corresponding tetrahydroisoindazole derivatives **7a** and **7b**, respectively.[4]



4 **5** **6** **7**

Compound	R_1	R_2	Reaction conditions		Yield %	Regio-selectivity **6** : **5**	m.p. °C
6a	CH_3	Ph	A	i. Morpholine, PTSA ii. PhCOCl, Et_3N iii. CH_3NHNH_2, EtOH	34*	7 : 3	165-166
6b	Ph	H	B	i. NaH, HCO_2CH_3, THF ii. $PhNHNH_2$, AcOH	45*	9 : 1	114-115
7a	CH_3	Ph	C	i. nBuLi, THF. ii. MeNCS	60	-	122-124
7b	Ph	H	C	i. nBuLi, THF. ii. MeNCS	44	-	173-174

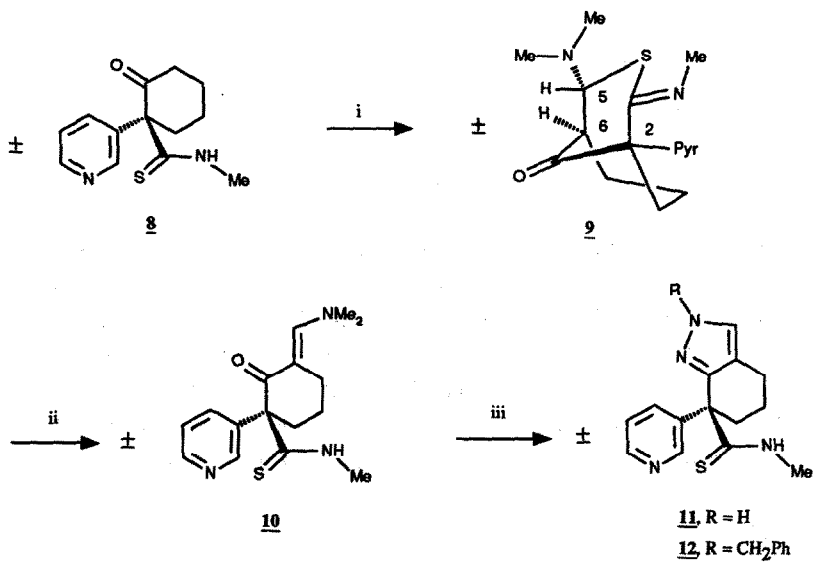
* = Combined yield of **5** and **6**

Scheme 2

Although this methodology was effective, it could not be used for the preparation of optically pure material owing to the lack of stereochemical control during the acylation step. Therefore, because we had recently developed[3] an efficient enantioselective synthesis of the ketone thioamide, **1**, we decided to investigate its conversion to compounds of the type **3** (X = N) using methodology which should, on mechanistic grounds, be non-racemising and, moreover, be compatible with an unprotected thioamide group. However, because we considered that the latter condition would be more difficult to fulfil, our initial studies were performed on the readily available, racemic ketone thioamide, **8**, (Scheme 3).[2]

Our first attempt to prepare the synthetically attractive enaminone **10**, by reaction of **8** with tris(dimethylamino)methane under standard conditions,[5] did not give the expected adduct, but afforded instead the unusual bicyclic [3.3.1] compound **9** (m.p. 150-151°C, >95%), which crystallised from the reaction mixture in essentially quantitative yield. Analysis of the ^{1}H n.m.r. spectrum of **9** established that the two vicinal carbon hydrogen bonds, C_5H and C_6H, are orthogonal[6a] and that the bicyclic system adopts a conformation in which the dimethylamino substituent resides in an equatorial orientation. The relative stereochemistry of the two newly created centres of asymmetry at C_5 and C_6 tends to be consistent, therefore, with an intramolecular nucleophilic attack by the thioamide group on an intermediate (E)-enaminone, **10**.

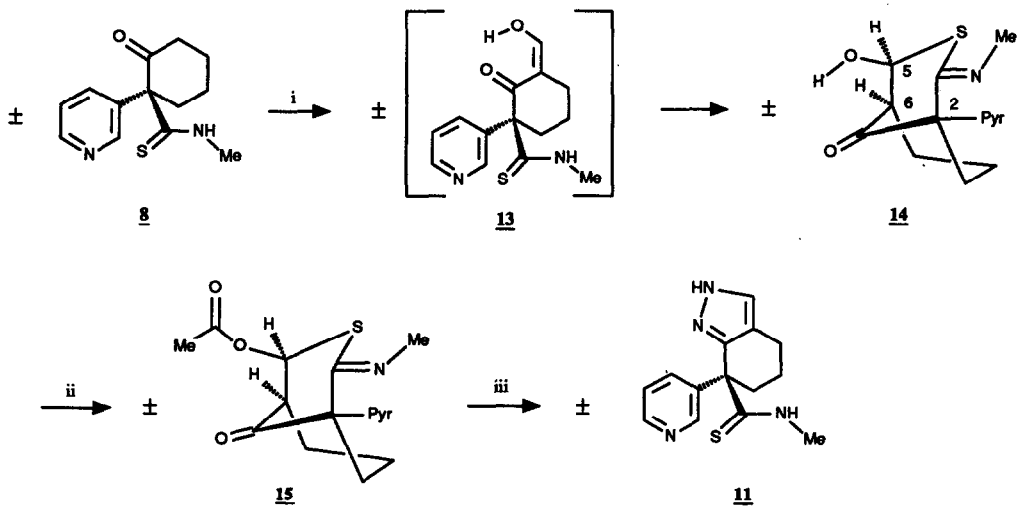
Ring opening of **9** was readily accomplished under mild acid conditions to yield (E)-**10** quantitatively (m.p. 130-132°C) and subsequent condensation of **10** with hydrazine or benzylhydrazine[7] furnished the desired heterocycles **11** (m.p. 225-227°C; 35%) and **12** (m.p. 94°C dec.; 47% as HCl salt) respectively.



i. $HC(NMe_2)_3$, THF, 60°C ii. HCl (0.05N), $CHCl_3/CH_3OH$, 25°C
iii. NH_2NH_2, CH_3OH, 25°C or $PhCH_2NHNH_2$, $CHCl_3/CH_3OH$, 25°C

Scheme 3

With the aim of exploring further the scope of this unusual intramolecular thioamide participation reaction, the synthetic sequence depicted in Scheme 4 was carried out. Thus, reaction of **8** with methyl formate under basic conditions[8] afforded directly the bicyclic adduct **14** (m.p. 214-216°C, 70%). An analysis of the ^{1}H n.m.r. spectrum of **14** revealed that the hydroxyl group at C_5 adopts an axial orientation.[6b] It is probable, therefore, that the intramolecular addition of the thioamide group occurs on the hydrogen bonded intermediate (Z)-**13**.



8 13 14 15 11

i. HCO_2CH_3, tBuOK, THF, 0°C ii. Ac_2O, 100°C iii. NH_2NH_2, CH_3OH

Scheme 4

In contrast to **9**, the adduct **14** was found to be stable to mild acid treatment, and, although it could not be directly ring opened by hydrazine, a smooth ring opening reaction could be achieved, following the conversion of **14** to the acetate **15** (m.p.186-188°C; 72%), to afford **11** as the sole product.

In summary, functionalised tetrahydroisoindazoles of the type **3** (X = N) have been prepared by two routes, which are compatible with the synthetically versatile, unprotected thioamide function. Moreover, because the absolute configuration of the centre of asymmetry should remain unaffected during the formation of **3** (X = N) *via* **10** or **15**, an asymmetric synthesis starting from **1** should now also be feasible.

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4. All new compounds gave satisfactory elemental and spectroscopic analyses. Yields were not optimised.
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6. a) $J_{5H,6H} = 0$ Hz. b) $J_{5H,6H} = 10.5$ Hz.
7. For related reactions see: a) Huff J.R., Baldwin J.J., de Solms S.J., Guare J.P., Hunt C.A., Randall W.C., Sanders W.S., Smith S.J., Vacca J.P. and Zrada M.M., *J. Med. Chem.*, 1988, 31, 641.
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