NEW HETEROCYCLIC ANALOGUES OF PYRIDOCARBAZOLES FROM AZIDOACRYLATES

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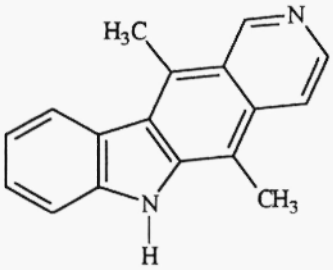
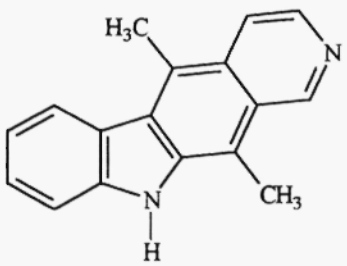
ABSTRACT: The thermal decomposition of azidoacrylates, prepared by condensation of ethyl azidoacetate with heteroaromatic aldehydes, gives rise to a series of new heterocyclic analogues of isoellipticine.

INTRODUCTION

In recent years several substituted pyrido[3,4-*b*]carbazoles have been synthesized and evaluated for biological activity (1). Among them was the 5,11-dimethyl-10*H*-pyrido[3,4-*b*]carbazole (Isoellipticine), an ellipticine isomer (2).

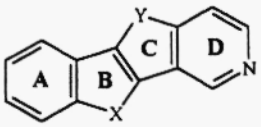


Ellipticine



Isoellipticine

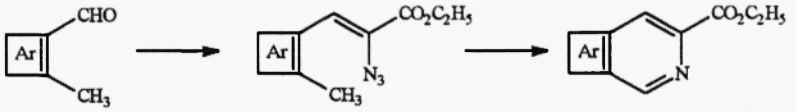
In a precedent paper, we described the synthesis of new biheterocyclic analogues of ellipticine *via* Pomeranz-Fritsch cyclisation (3). We present here the synthesis of a number of new isoellipticine analogues obtained by replacing pyrrole and benzene rings (rings B and C) by other heterocycles like thiophene and selenophene. These heterocyclic analogues will have the general structure I:



I

X, Y = S, Se

Our strategy was based on the work of Rees and Rodrigues (4). They have reported a simple and general procedure for pyrido-annelation under neutral conditions. This method, which involves formation of the 1-2 bonds in the ring closure step, is based on readily available vinyl azides which decompose thermally (in toluene, xylene or bromobenzene) to give different fused pyridines and isoquinolines (Scheme 1).

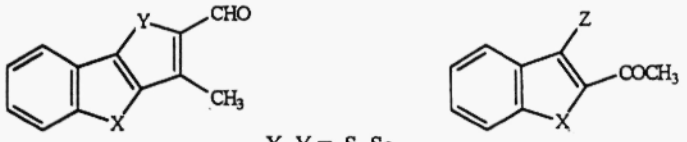


Ar = Aromatic or heteroaromatic cycle

Scheme 1

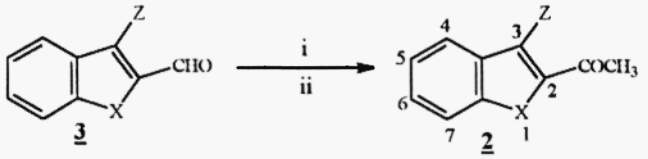
RESULTS AND DISCUSSION

In our case, the formation of the isoquinoline ring (ring D in structure I) from azidoacrylates, will be applied onto the tricyclic aldehydes 1. Hence, a series of heterocyclic compounds 1 was synthesized, after many steps, from halo-ketones 2.



1 X, Y = S, Se; Z = Br, Cl 2

Compounds 2 were prepared via Grignard reagents (Scheme 2). The Grignard reaction of the aldehydes 3 with iodomethylmagnesium furnished the secondary alcohols which provided the desired ketones 2 after oxidation. Several oxidants were tested: Corey's reagent (5), Jones reagent (6) and pyridinium dichromate. Jones reagent used in large excess gave the best results.



Reagents and conditions: i, CH_3I, Mg, ether, reflux; ii, $HCrO_4$-acetone (Jones reagent).

Scheme 2

Table I shows chemical data for compounds 2.

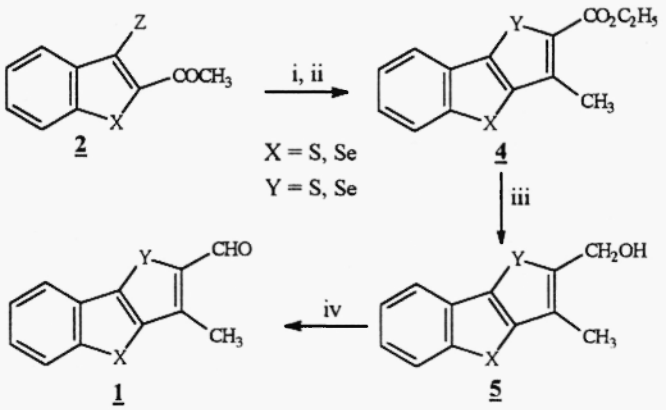
Table I: Haloketones 2

X	Z	Mp (°C) (Lit.) (Recrystallisation solvent)	Yields (%)	^{1}H NMR ($CDCl_3$)* δ (ppm) and multiplicity**
S	Br	100(98) (EtOH)	65	2.82 (3H, s, $COCH_3$); 7.48-7.52 (2H, m, ArH); 7.82 (1H, d, J 7.52, ArH); 7.97 (1H, d, J 7.60, ArH)
Se	Cl	100(97) (MeOH)	55	2.84 (3H, s, $COCH_3$); 7.46-7.51 (2H, m, ArH); 7.87 (1H, d, J 9.00, ArH); 8.00 (1H, d, J 9.27, ArH)

* With TMS as internal standard

** Abreviations have their usual significance

Condensation of ketones 2 with sodium sulfide (Y = S) or selenide (Y = Se) and ethyl bromo (chloro)acetate afforded, after esterification, esters 4 (Table II). Reduction of compounds 4 by lithium aluminum hydride furnished alcohols 5 (Table III) which after oxidation with Corey's reagent provided the tricyclic aldehydes 1 (Table IV) in good yields (Scheme 3).



Reagents and conditions: i, Na_2Y (Y = S or Se), DMF, $ClCH_2CO_2C_2H_5$ or $BrCH_2CO_2C_2H_5$; ii, H_2SO_4, ethanol abs., reflux; iii, $LiAlH_4$, ether, reflux; iv, PCC, CH_2Cl_2

Scheme 3

Table II: Esters 4

X	Y	Mp (°C) (Recrystallisation solvent)	Yield (%)	Anal.Found/Calcd. (%) C	H	^{1}H NMR ($CDCl_3$) δ (ppm) and multiplicity
S	S	107 (ether)	56	60.78 60.87	4.30 4.35	1.43 (3H, t, J 7.0, CH_3); 2.71 (3H, s, CH_3); 4.40 (2H, q, J 7.1, CH_2); 7.42 (1H, d, ArH); 7.44 (1H, d, ArH); 7.87 (2H, m, ArH)
S	Se	100 (dichloromethane/ pet. ether)	40	52.16 52.01	3.77 3.71	1.41 (3H, t, J 7.3, CH_3); 2.69 (3H, s, CH_3); 4.37 (2H, q, J 7.38, CH_2); 7.42 (1H, d, ArH); 7.44 (1H, d, ArH); 7.85 (1H, m, ArH); 7.88 (1H, m, ArH)
Se	Se	125 (ethylacetate/ pet. ether)	35	45.64 45.40	3.18 3.24	1.41 (3H, t, J 7.2, CH_3); 2.68 (3H, s, CH_3); 4.38 (2H, q, J 7.23, CH_2); 7.35 (1H, d, J 7.05, ArH); 7.43 (1H, t, J 7.17, ArH); 7.84 (1H, d, J 7.30, ArH); 7.94 (1H, d, J 7.84, ArH)

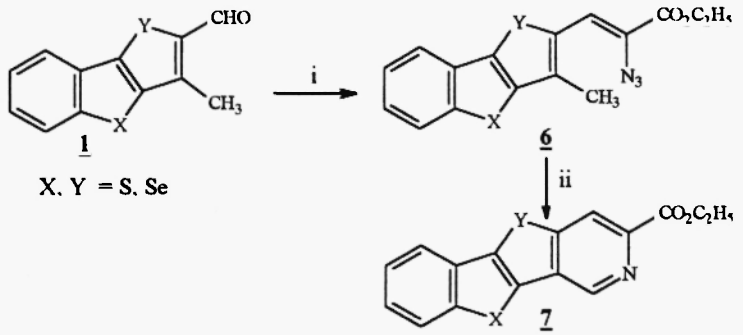
Table III: Alcohols 5

X	Y	Mp (°C) (Recrystallisation solvent)	Yield (%)	Anal.Found/Calcd. (%) C	H	^{1}H NMR ($CDCl_3$) δ (ppm) and multiplicity
S	S	135 (ether)	55	61.37 61.54	4.22 4.27	1.97 (1H, s, OH); 2.36 (3H, s, CH_3); 4.85 (2H, s, CH_2); 7.32-7.37 (2H, m, ArH); 7.80 (1H, d, J 7.60, ArH); 7.85 (1H, d, J 7.88, ArH);
S	Se	156 (ether)	55	51.22 51.24	3.70 3.56	2.17 (1H, s, OH); 2.55 (3H, s, CH_3); 4.75 (2H, s, CH_2); 7.24 (2H, m, ArH); 7.64 (1H, d, J 7.60, ArH); 7.75 (1H, d, J 7.80, ArH);
Se	Se	141 (ether)	60	44.02 43.90	3.23 3.05	2.16 (1H, s, OH); 2.53 (3H, s, CH_3); 4.75 (2H, s, CH_2); 7.15-7.29 (2H, m, ArH); 7.63 (1H, d, J 7.57, ArH); 7.80 (1H, d, J 7.77, ArH);

Table IV: Tricyclic aldehydes 1

X	Y	Mp (°C) (Recrystallisation solvent)	Yield (%)	Anal.Found/Calcd. (%) C	H	^{1}H NMR ($CDCl_3$) δ (ppm) and multiplicity
S	S	180 (ether)	70	62.16 62.07	3.24 3.44	2.71 (3H, s, CH_3); 7.44 (1H, d, ArH); 7.46 (1H, d, ArH); 7.90 (2H, m, ArH); 10.11 (1H, s, CHO)
S	Se	176 (ether)	70	51.50 51.61	3.05 2.87	2.68 (3H, s, CH_3); 7.45 (2H, m, ArH); 7.88 (2H, m, ArH); 10.02 (1H, s, CHO)
Se	Se	175 (ether)	53	44.33 44.17	2.60 2.45	2.67 (3H, s, CH_3); 7.35-7.48 (2H, m, ArH); 7.89 (1H, d, J 8.25, ArH); 7.93 (1H, d, J 7.50, ArH); 10.00 (1H, s, CHO)

The vinyl azides 6 were obtained by the condensation of the heteroaromatic aldehydes 1 with ethyl azidoacetate (4 equiv.) in ethanolic sodium ethoxide (7). Better yields were obtained when the condensation was carried out between -10 °C and room temperature (Scheme 4).



Reagents and conditions: i, $N_3CH_2CO_2C_2H_5$, $NaOC_2H_5$, -10 °C-r.t.; ii, heat, toluene

Scheme 4

The stereochemistry of the double bond in compounds 6 is not known. The geometry about it does not matter, since vinyl azides decompose *via* 2H-azirines which are in thermal equilibrium with the corresponding vinyl nitrenes. Stereochemistry is lost during the reaction.

Table V contains the different vinyl azides 6 prepared.

Table V: Vinyl azides 6

X	Y	Mp (°C)	Yield (%)	^{1}H NMR ($CDCl_3$) δ (ppm) and multiplicity
S	S	115	56	1.42 (3H, t, CH_3); 2.48 (3H, s, CH_3); 4.40 (2H, q, CH_2); 7.40-7.43 (2H, m, ArH); 7.52 (1H, s, CH); 7.86-8.00 (2H, m, ArH)
S	Se	120	48	1.41 (3H, t, CH_3); 2.47 (3H, s, CH_3); 4.38 (2H, q, CH_2); 7.33-7.42 (2H, m, ArH); 7.50 (1H, s, CH); 7.85-7.88 (2H, m, ArH)
Se	Se	118	60	1.44 (3H, t, CH_3); 2.52 (3H, s, CH_3); 4.45 (2H, q, CH_2); 7.37 (1H, m, ArH); 7.46 (1H, m, ArH); 7.53 (1H, s, CH); 7.88 (1H, d, J 7.50, ArH); 7.92 (1H, d, J 7.88, ArH)

Thermal decomposition of vinyl azides (used without further purification) is carried out in neutral conditions. Non polar solvents are used: bromobenzene, toluene,... In our case, the azides 6 were decomposed in boiling toluene to give, after chromatography, a new tetracyclic analogue of isoellipticine 7 (Table VI).

Table VI: Isoellipticine analogues 7

X	Y	Mp (°C) (Recrystallisation solvent)	Yields (%)	Anal.Found/Calcd. (%) C	H	N	^{1}H NMR ($CDCl_3$) δ (ppm) and multiplicity
S	S	198 (dichloromethane/ ethylacetate)	43	61.50 61.34	3.50 3.51	4.12 4.47	1.50 (3H, t, CH_3); 4.55 (2H, q, CH_2); 7.50 (2H, m, ArH); 7.92 (1H, d, J 6.5, ArH); 7.95 (1H, d, J 6.4, ArH); 8.72 (1H, s, ArH); 9.24 (1H, s, ArH)
S	Se	192 (dichloromethane/ ethylacetate)	45	53.20 53.33	2.98 3.05	3.76 3.88	1.51 (3H, t, CH_3); 4.53 (2H, q, CH_2); 7.47-7.51 (2H, m, ArH); 7.88 (1H, t, J 8.00, ArH); 7.94 (1H, t, J 7.80, ArH); 8.70 (1H, s, ArH); 9.20 (1H, s, ArH)
Se	Se	215 (dichloromethane/ ethylacetate)	40	47.02 47.17	2.63 2.70	3.39 3.44	1.53 (3H, t, CH_3); 4.57 (2H, q, CH_2); 7.45 (1H, t, J 7.65, ArH); 7.54 (1H, t, J 7.70, ArH); 7.95 (1H, d, J 7.70, ArH); 8.04 (1H, d, J 7.66, ArH); 8.68(1H, s, ArH), 9.23 (1H, s, ArH)

CONCLUSION

Formation of the pyridinic ring D *via* azidoacrylates provides a route to different biheterocyclic analogues of isoellipticine from ortho-alkylated heteroaromatic aldehydes. This synthetic method is easy to carry out. Ring D is formed under neutral conditions to provide compounds 7 in moderate yields.

EXPERIMENTAL

All the melting points were determined on a Kofler bench and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 250 MHz spectrometer ($CDCl_3$, TMS as internal standard).

Compounds 3, 4 were prepared by known methods (3, 8).

Preparation of ketones 2

A solution of CH_3MgI (4 equivalents) in dry ether was slowly added to a solution (1 equivalent) of aldehyde 3 at a rate such as to keep a gentle reflux. The mixture was refluxed for 90 min. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether and the organic layer dried over Na_2SO_4. After evaporation of the solvent, the obtained oil (1 equivalent) was dissolved in acetone. 2.67 M-Jones reagent (3 equivalents) (prepared by dissolving 26.7 g of CrO_3 in 23 ml of conc. H_2SO_4, diluted with water to a volume of 100 ml) was added to the solution, at 0 °C

and the reaction mixture was stirred for 90 min at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethylacetate. After evaporation of the solvent, the crude product was purified by recrystallisation (Table I).

Preparation of alcohols **5**

0.01 mol (1 equivalent) of ester **4** was slowly added to a solution of 0.025 mol (2.50 equivalents) of lithium aluminum hydride in 30 ml of dry ether. The mixture was then refluxed for 3 hours. After cooling to room temperature, the reaction mixture was poured onto an ice cooled solution of 20% H_2SO_4 and extracted with ether. The crude alcohol was purified by recrystallisation (Table III).

Preparation of aldehydes **1**

To a suspension of (0.015 mol) of PCC (5) in (26 ml) CH_2Cl_2 was added one portion (0.01 mol) of alcohol **5** in (26 ml) CH_2Cl_2. The reaction mixture was stirred at room temperature for 3 hours and extracted 4 times with dry ether. The combined extracts were filtered on silica gel. After evaporation the crude product was purified by recrystallisation (Table IV).

Preparation of azides **6**

(0.08 g-atom) of sodium was dissolved in (55 ml) of ethanol and the solution was cooled to -10 °C. A mixture of (0.02 mol) of the aldehyde **1** and (0.08 mol) of ethyl azidoacetate was added dropwise with stirring at a rate such as to keep the temperature below -10 °C. (If the aldehyde was insoluble in ethylacetate, sufficient tetrahydrofurane was added to achieve complete dissolution). The reaction mixture was stirred at room temperature until t.l.c. indicated that all the aldehyde had been consumed (2-3 h). The mixture was poured onto ice-water. After filtration the crude azide was purified by recrystallisation (Table V).

Preparation of tetracycles **7**

A solution of the azide **6** (5.3 mmol) in toluene (15 ml) was refluxed until t.l.c. showed that all the azide had been consumed (4 h). The solvent was evaporated and the crude product was purified by chromatography on silica gel using dichloromethane: ethylacetate (8:2) as eluent (Table VI).

Acknowledgements

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