Diels-Alder in heterocyclic synthesis : a novel synthesis of cycloalkanopyridazinimine, 1,7-alkanothienopyridazines and 1,8-alkanophthalazines: new ring system

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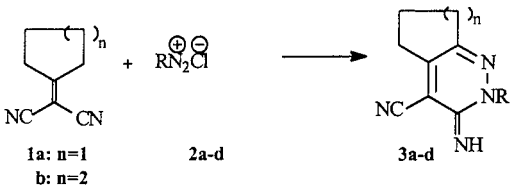
Transformation of the newly synthesized alkano[*c*]pyridazines and 1,7 propanothienopyridazines into 1,8-propanophthalazinones and 1,9-propanothiepinopyridazinones using [4+2] cycloaddition reaction with electron poor olefins and acetylenedicarboxylate derivatives, respectively is described.

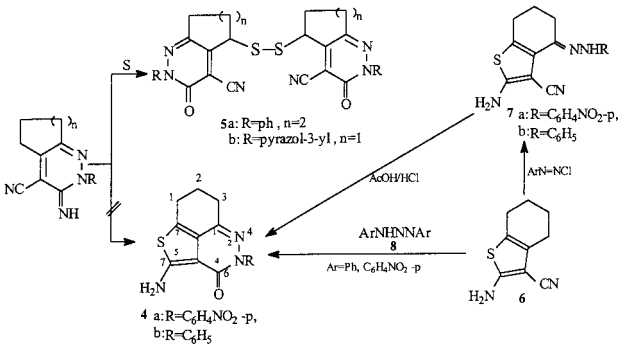
One of the most important reaction in organic chemistry for the formation of carbon–carbon bonds is the Diels-Alder reaction and much effort has been devoted to the development of this reaction in recent years.[1-3] In this area, thiophenes are highly inactive as a diene.[4,5] Thienopyridazine derivative have shown that the electron poor olefins readily add to yield cycloadducts that readily decompose or rearrange into phthalazines or thiepins, depending on both the nature of the olefin and the applied reaction condition[10]. Here we report the synthesis of cycloalkano[*c*]pyridazinimine and thienopyridazinone derivatives as building bocks propanophthalazinone and thiepenopyridazinone deivatives, that are required for testing in our biological program.Thus, treatment of ylidenemalononitrile **1a,b** with diazonium salts **2a-d** in sodium hydroxide afford the corresponding pyridazine-3-imines **3a-d** in excellent yield. The structure of compounds **3a-d** were confirmed by analytical and spectral data. Thus, IR spectra showed sharp band at 2,212–2,180 cm^{-1} characteristic of the stretching frequency of nitriles and bands for NH in the region 3,266–3,410 cm^{-1}. Moreover, the MS spectrum of **3a** shows *m/z* = 250 (M^+) and its ^{13}C NMR spectrum is in complete agreement with the proposed structure (Scheme 1). The formation of **3a-d** is further extension for synthesis of condensed pyridazine by our laboratories.[11,12]



2,3	R	n
a	Ph	2
b	$C_6H_4NO_2(p)$	2
c	$C_6H_4OCH_3(p)$	2
d	N–NH, CH_3	1

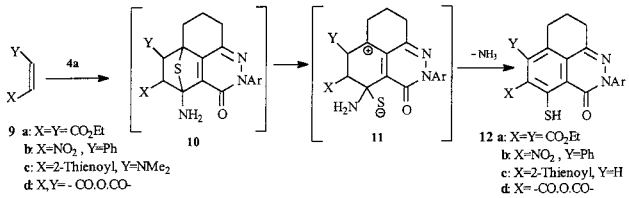
Scheme 1

Compounds **3a** and **3b** reacted with sulfur in ethanolic triethylamine afforded 5,5′-dithiobis(cycloalkanopyrid-azines) 5a,b. The isolated products were established based on elemental analysis and spectral data. As a consequence of this result we tried to synthesise thienopyridazine **4**. Thus, treatment of compound **6** with aryldiazonium salts in strong basic medium furnished a single product, identified as acyclic hydrazone **7** which was converted into thienopyridazine **4**, in low yield, upon reflux in acetic acid / hydrochloric acid mixture. The structure of **4** was established on the basis of its elemental analysis and spectral data besides an independent synthesis from compound **6** and diazoaminobenzene derivatives **8a,b** to afford a product, in excellent yield, identical in all respects (m.p. and spectra) with that obtained previously upon refluxing **7** in acidic medium.



Scheme 2

Compound **4a** reacts with olefins **9a-d** in refluxing dioxane given 1,8-propanophthalazine **12a-d** *via* a new reaction path way. Compounds **12a-d** were assumed to be formed *via* intermediacy **10** and **11**. It seems that under such conditions, loss of ammonia, and not hydrogen sulfide elimination, is the predominating reaction path way. At the same time, compound **12c** was formulated upon loss of both ammonia and dimethylamine molecules.



Scheme 3

Compounds **4a** and **4b** reacted with dimethyl or diethyl acetylene-dicarboxylate to yield thiepin derivatives **16a,b** which is believed to be formed *via* the non isolated intermediates **13, 14** and **15** (*cf.* Scheme 5). Similar formation of thiepins has been reported from our laboratories[8] as well as Dopp *et al*.[7] All trials to prepare compounds **17a,b** from **16a,b** failed even upon heating above their melting point.

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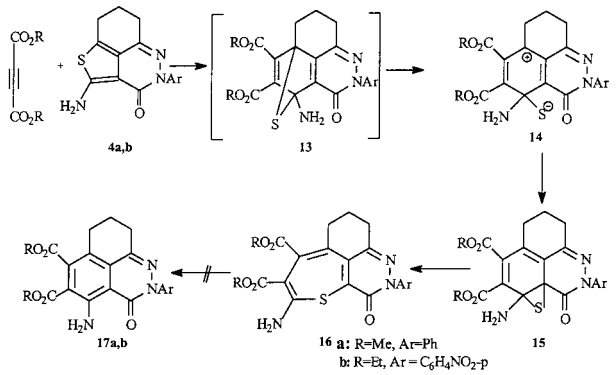
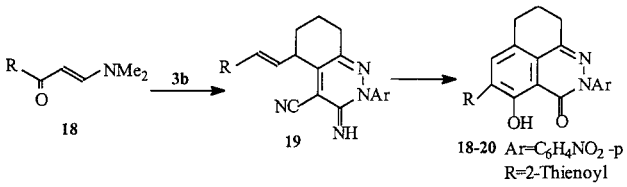


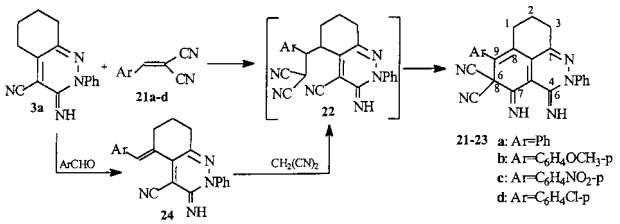
Scheme 4

Compound **3b** could also be reacted with enaminone **18** in basic medium to afford the acyclic compound **19** via loss of a dimethylamine molecule. The latter then cyclized into **20** on boiling in a mixture of aqueous acetic acid and hydrochloric acid. Compound **20** could also be obtained via direct reaction between **3b** and **18** in aqueous acetic acid /hydrochloric acid mixture. The structure of compounds **19** and **20** were established on the basis of their elemental analysis and spectral data.



Scheme 5

The ring system **23** could also be obtained in a good yield when cyclohexapyridazine **3a** reacted with arylidenemalononitrile derivatives **21a-d**, in basic medium. The same reaction products **23a-d** could also be obtained when **3a** reacted with an aromatic aldehyde followed by treatment the reaction mixture with malononitrile *in situ*. The structures of the reaction product were established based on their elemetal analysis and spectral data.



Scheme 6

Techniques used: IR, ^{1}H and ^{13}C NMR, MS

References: 15

Schemes: 6

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