A Novel Synthesis of Cyclopenta[*c*]pyridazines and 1,8-Ethanophthalazinones: A New Ring System

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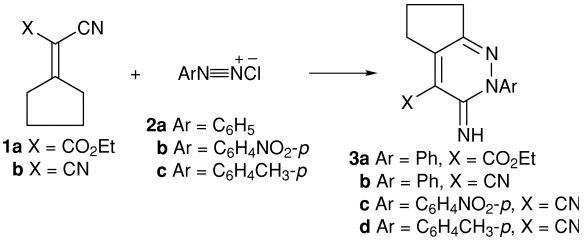
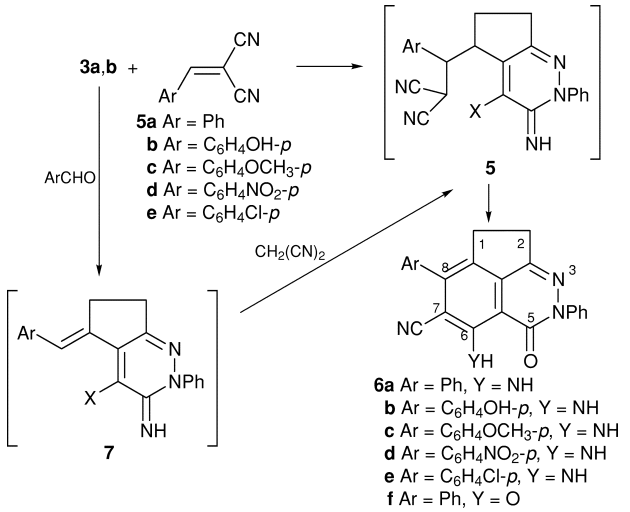
The synthesis of 1,8-ethanophthalazine derivatives from reaction of cyclopenta[*c*]pyridazines with arylidenemalononitrile or active methylene nitriles is described.

Polyfunctionally substituted phthalazinones and their fused derivatives comprise a very interesting class of compounds because of their significant biological and pharmaceutical activities.[1–4] Here we report the synthesis of cyclopentapyridazinone and cyclopentapyridazinimine derivatives as building blocks for the synthesis of ethanophthalazinone derivatives, that are required for testing in our biological program. Thus, cyclopentylidene derivatives **1a**,**b** readily coupled with aryldiazonium salts **2a**–**c** in basic media to give **3a**–**d** (Scheme A). The structures of compounds **3** were established based on elemental analysis and spectral data. For example, the MS spectrum of **3a** shows *m*/*z* 283 and its IR spectrum reveals the presence of NH and carbonyl groups at 3287 and 1720 cm^{-1}, respectively. However, ^{13}C NMR indicates the absence of a cyano group and the presence of a carbonyl group at δ 161.21 and other skeletal carbons at expected positions. In addition this, ^{1}H NMR shows expected signals. Similarly, the structure of **3b** was established based on elemental and spectral data. MS indicates the molecular formula $C_{14}H_{12}N_4$ ($m/z = 236$). IR reveals the presence of NH and cyano groups at 3332 and 2216 cm^{-1}, respectively. In addition ^{13}C NMR shows only one cyano group at δ 113.61 and other skeletal carbons at expected positions. Similarly, compounds **3c**,**d** were also established.



Scheme A

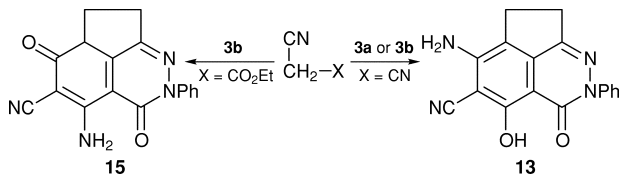
Compounds **3a**,**b** reacted with arylidenemalononitriles **4a**–**e** in ethanolic piperidine to give **6a**–**f** (Scheme B). Compounds **6a**–**f** are assumed to be formed *via* Michael addition, where active methylene in cyclopentylidene added to the double bond in arylidene derivatives to give the intermediate **5**. The latter cyclized and then aromatized by loss of HCN to give the final isolated products **6a**–**f** (Scheme B). The structure of **6** was established based on spectral data. Whereas the MS of **6a** and **6f** showed molecular formulae $C_{23}H_{16}N_4O$ ($m/z = 364$) and $C_{23}H_{15}N_3O_2$ ($m/z = 365$), respectively, ^{13}C NMR of **6a** reveals the presence of one cyano function at δ 112.78 and CO at δ 164.89 in addition to other skeletal carbons. Similarly, compounds **6b**–**f** were established. Compounds **6a**–**f** could also be prepared by Knoevenagel condensation of **1a**,**b** with the aromatic aldehyde followed by treatment with malononitrile *in situ* to give the final isolated products **6a**–**f** (Scheme B).



Scheme B

The target ring system could also be obtained on treatment of **3a** with active methylene nitriles. Thus, **3a** or **3b** reacted with malononitrile in basic media to give **13** (Scheme C). Compound **13** is believed to be formed *via* addition of the active methylene of the cyclopentylidene ring to the cyano group in malononitrile and then obtained by cyclization *via* elimination of ethanol or ammonia. The structure of **13** was established based on the mixed melting point of the product obtained from **3a** with malononitrile and that from **3b** with the same reagent, as well as elemental analysis, and spectral data. For example MS indicates a molecular formula $C_{17}H_{12}N_4O_2$ ($m/z = 304$). ^{1}H NMR revealed the absence of triplet and quartet signals of the ethyl ester group. ^{13}C NMR shows the presence of one cyano group and a carbonyl group at δ 112.12 and 162.00 respectively.

On the other hand, ethyl cyanoacetate reacts with **3b** in ethanolic piperidine to give **15** (Scheme C). Compound **15** was established based on ^{1}H NMR which revealed the absence of an ethyl group, and IR spectroscopy which revealed the presence of amino, cyano and carbonyl groups at 3342, 3241; 2207 and 1734, 1651 cm^{-1}, respectively.



Scheme C

Compound **3b** reacts with acetylacetone or ethyl acetoacetate in ethanolic triethylamine to afford the condensation products **16a**,**b** (Scheme D). All attempts to cyclize **16a**,**b**

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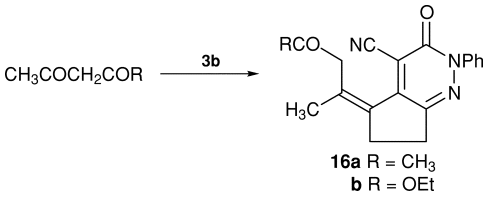

Scheme D

in acidic media (*e.g.* acetic acid or acetic acid–hydrochloric acid), or in basic media, (pyridine), or even on heating without solvent to a temperature slightly above their melting point were unsuccesful. Compound **16a** was established based on elemental and spectral data. IR reveals the presence of cyano group at 2203 and two carbonyl bands at 1725 and 1688 cm^{-1}. Similarly, compound **16b** was established as a reaction product.

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

References: 14

Schemes: 6

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