Difunctional heterocycles: a convenient synthesis of bis(pyridinyl-2,3-dihydrooxadiazolyl)benzenes

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Bis(pyridinyl-2,3-dihydrooxadiazolyl)benzenes **5a-e** and **9a, b** are obtained in 25-85% yields by heating the corresponding bis(hydrazones) **4a-f** and **8a, d** in refluxing Ac_2O–AcOH for 3–5 h, while the bishydrazones **19** and **17b** give 33–54% yields of the phthalazine derivatives **20a, b** upon heating in refluxing ethanol containing acetic acid.

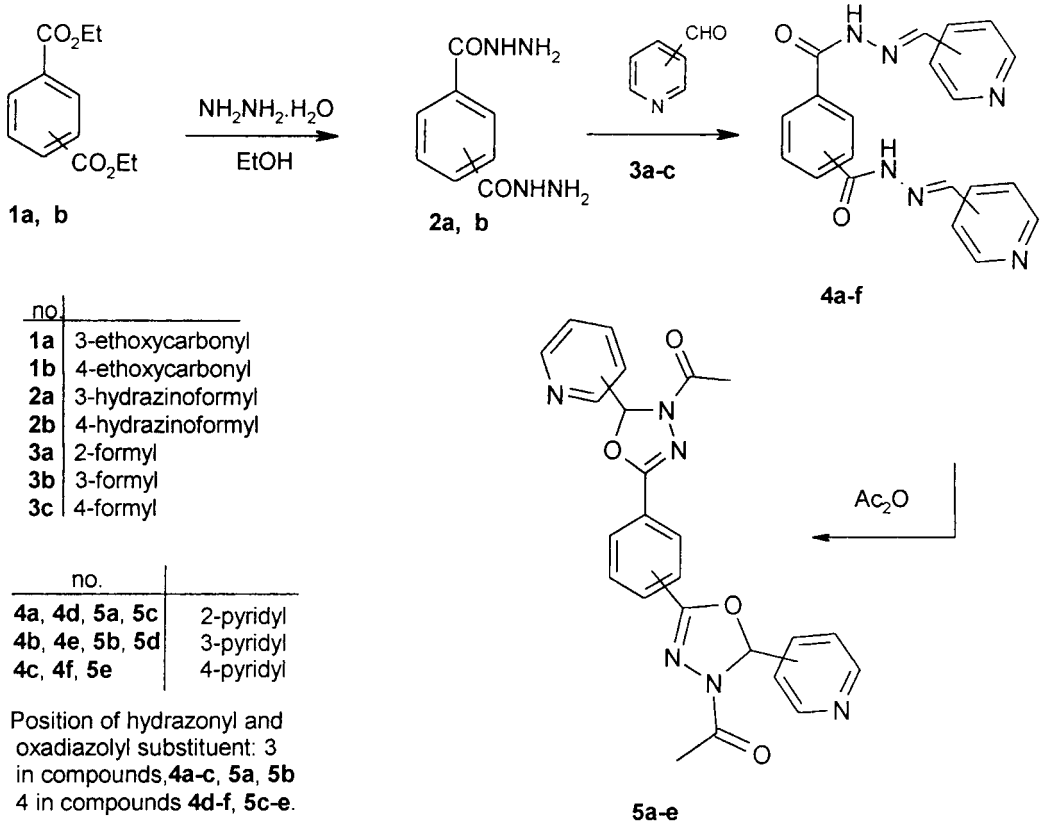
Keywords: difunctional heterocycles, bis(pyridinyl-2,3-dihydrooxadiazolyl) benzenes

There is a continuous interest in the chemistry of 1,3,4-oxadiazoles on account of their biological properties – bactericidal,[1] fungicidal,[2] antimicrobial,[3] antiinflammatory,[4] and antiproteolytic,[5] for example. In addition, pyridines are reported to exhibit diverse biological activities as antimycotic,[6] antidepressant,[7] and antiarrhythmic[8] agents. The presence of these two rings in one molecule might combine the biological activities of both moieties.

In connection with these findings and in continuation of our recent interest in the synthesis of bis-difunctional building blocks to study their use in the synthesis of bisheterocycles,[12–14] we report here on the synthesis of novel isomeric bis(pyridinyldihydrooxadiazolyl)benzene derivatives. During the last decades such compounds have attracted attention not only as model compounds for polymers but also because many biologically active natural and synthetic products have molecular symmetry.[21] We also discuss the formation of unexpected products in some reactions.

Our strategy to synthesise the new bis(2,3-dihydro-2-pyridinyloxadiazol-5-yl)benzene derivatives **5a–e** is outlined in Scheme 1. Thus, reaction of diethyl isophthalate (**1a**) or diethyl terephthalate (**1b**) with hydrazine hydrate in refluxing ethanol afforded the corresponding bis(hydrazides) **2a, b**.[22] Condensation of the latter with the appropriate pyridinecarboxaldehyde **3a–c** in refluxing ethanol afforded 88–95% yields of the corresponding bis(hydrazones) **4a–f**. Cyclisation of **4a, b** and **4d–f** to the bis(dihydrooxadiazolyl) derivatives **5a–e** was effected by heating in acetic anhydride and acetic acid.

Our study was extended to include the synthesis of the new isomeric bis(2,3-dihydro-5-pyridinyloxadiazol-2-yl)benzenes **9a, b** (Scheme 2). Thus, reaction of isopthalaldehyde (**6a**) and terepthalaldehyde (**6b**) with the appropriate pyridine



1a, b

2a, b

4a-f

5a-e

no	
1a	3-ethoxycarbonyl
1b	4-ethoxycarbonyl
2a	3-hydrazinoformyl
2b	4-hydrazinoformyl
3a	2-formyl
3b	3-formyl
3c	4-formyl

no.	
4a, **4d**, **5a**, **5c**	2-pyridyl
4b, **4e**, **5b**, **5d**	3-pyridyl
4c, **4f**, **5e**	4-pyridyl

Position of hydrazonyl and oxadiazolyl substituent: 3 in compounds,**4a-c**, **5a**, **5b** 4 in compounds **4d-f**, **5c-e**.

Scheme 1

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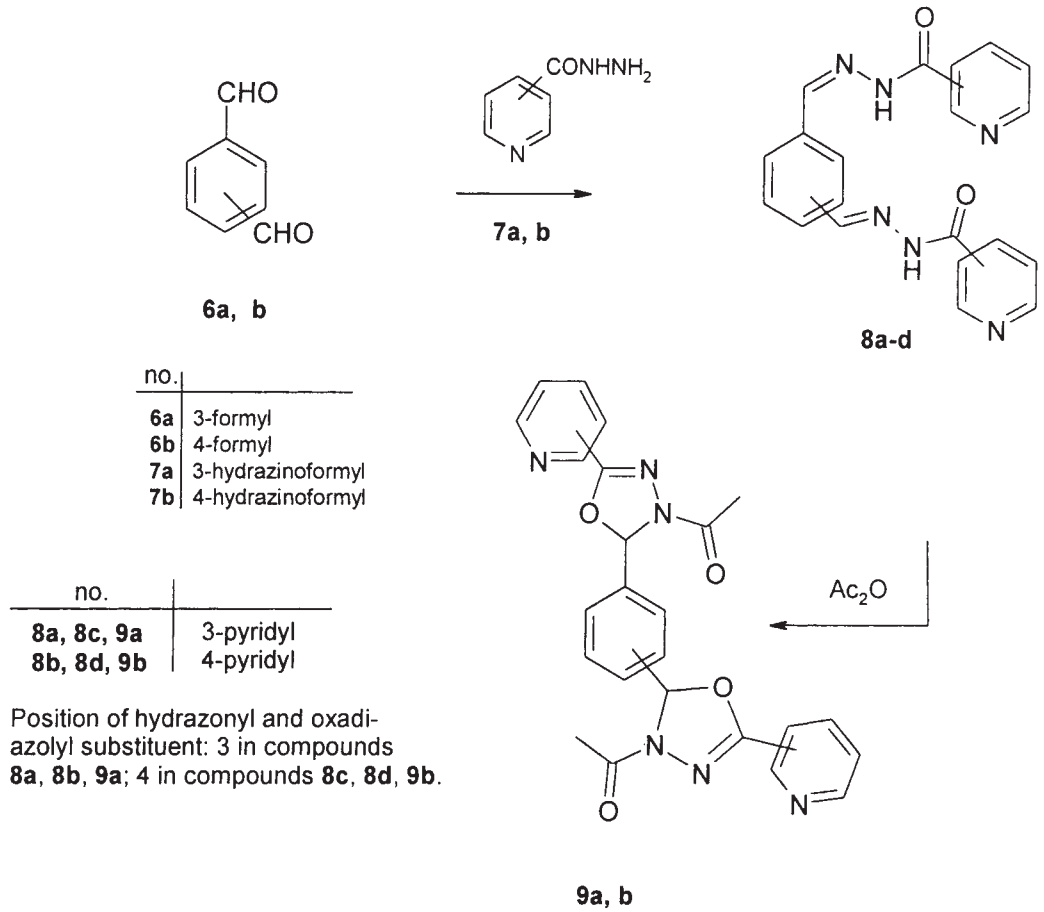


Scheme 2

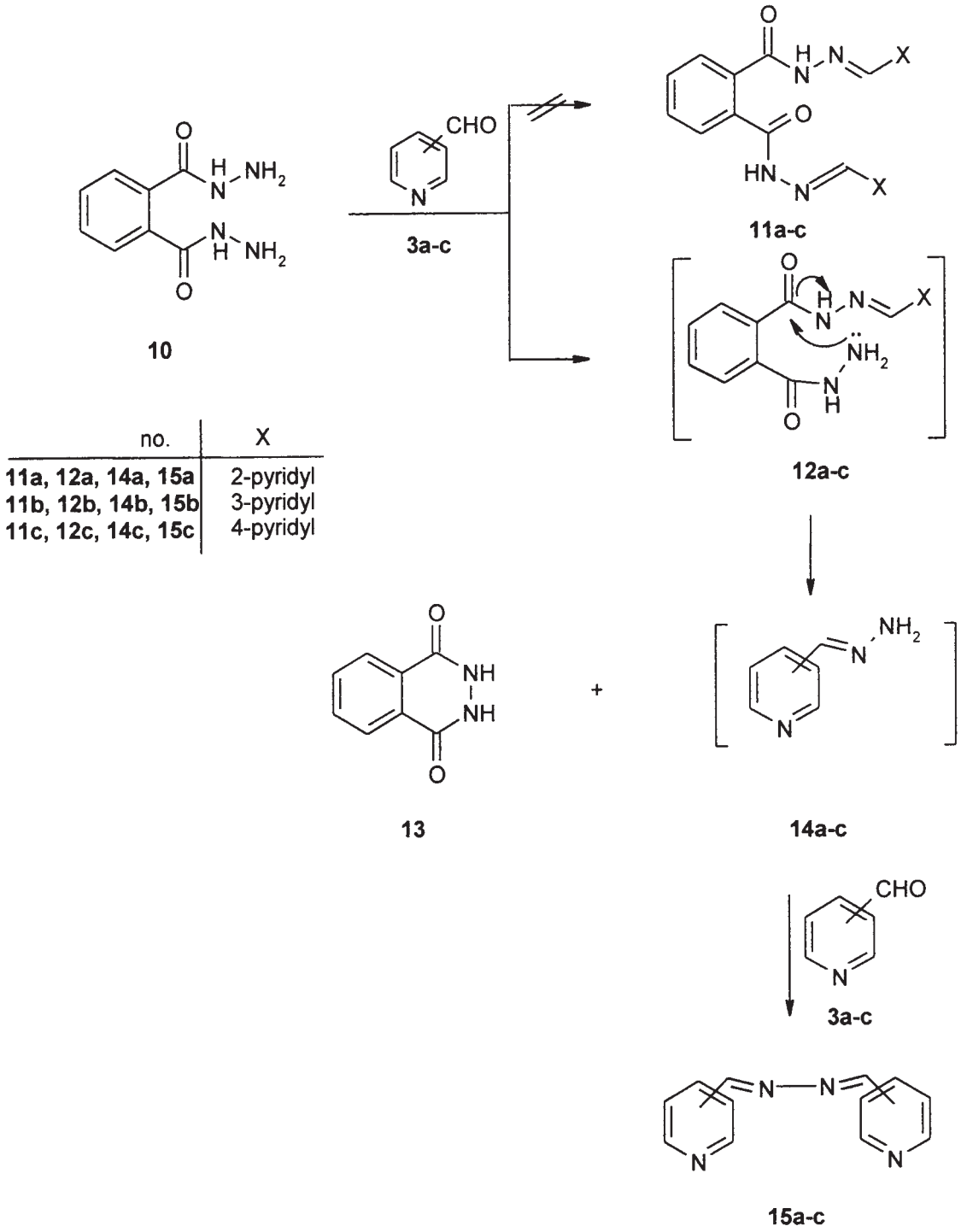
hydrazide **7a, b** in refluxing ethanol for 2–3 h. afforded the corresponding bis(hydrazones) **8a–d**, in 50–90% yields. Heating **8c, d** in refluxing Ac_2O–AcOH mixture for 3–5 h. afforded 25% and 27% yields, respectively, of the corresponding bis(dihydrooxadiazolyl)benzenes **9a, b**.

We also attempted to prepare the 1,2-bis(hydrazones) **11a–c** as key intermediates in the synthesis of new 1,2-bis(dihydrooxadiazolyl) benzene derivatives. Unfortunately, reaction of the 1,2-bis(hydrazinoform-yl)benzene (**10**) with the appropriate pyridine-carboxaldehydes **3a–c** in refluxing ethanol did not yield the expected bis(hydrazones) **11a–c**. Instead, the reaction gave mixture of phthalazine-1,4-dione (**13**) in 52% yield together with 25–40% yields of the corresponding bis-pyridinylmethylene hydrazine **15a–c**. The reaction proceeds *via* initial condensation of **10** with one equivalent of the appropriate pyridine-carboxaldehydes **3a–c** to give the corresponding monohydrazones **12a–c**. Attack of the amino group of the hydrazide on the carbonyl group of the hydrazones and subsequent elimination of the hydrazones **14a–c** (Scheme 3) led to the formation of **13**. The hydrazones **14a–c** react immediately under the reaction conditions with a further molecule of the corresponding pyridine carboxaldehyde **3a–c** to give **15a–c**.

Our study also includes the synthesis of the new bis(hydrazones) **17a, b** in 90 and 56% yields, respectively, by condensing *o*-phthaldialdehyde (**16**) with the appropriate pyridine hydrazides **7a, c**[29] respectively, in refluxing ethanol (Scheme 4). Repeated attempts to convert the bis(hydrazones) **17a, b** into the corresponding 1,2-bis(dihydrooxadiazolyl)benzenes **18a, b** by heating in refluxing Ac_2O–AcOH mixture were unsuccessful, presumably for steric reasons. The reaction gave instead a mixture of products that were not easily handled and could not be characterised.

On the other hand, reaction of **16** with the pyridin-4-yl hydrazide (**7b**) in refluxing ethanol failed to give a pure sample of the corresponding hydrazone **19**. The ^{1}H NMR spectrum of the reaction products indicated the presence of **19** together with a second product. This was supported by the presence of the molecular ion peak of **19** in the mass spectrum. All attempts to separate these compounds were unsuccessful. Heating the mixture of products in refluxing ethanol containing a few drops of acetic acid was found by ^{1}H NMR to enhance the formation of the second product with respect to the hydrazone **19**. After reflux for 1 h, the second compound could be isolated as the sole reaction product and it was characterized as the phthalazine derivative **20a**. This reaction provide a new and easy access to novel phthalazine derivatives. It presumably proceeds *via* initial formation of the corresponding bis(hydrazone) **19** followed by nucleophilic attack of the amine group (N-1) on the benzylideneamino carbon (C-6) under the experimental conditions. The reaction was facilitated by the enhanced electrophilicity of C-6 caused by protonation of N-6 under the acidic conditions. This reaction was confirmed by the possible formation of the phthalazine derivative **20b** upon heating the hydrazone **17b** in refluxing ethanol containing acetic acid.

The structures proposed for the new compounds **20a, b** are consistent with their elemental analyses, ^{1}H NMR, ^{13}C NMR and mass spectra. Thus, the ^{1}H NMR spectra of compounds **20a, b** revealed two doublet signals at δ 6.84 and δ 6.86 ppm, respectively, characteristic for the methinyl protons (H-6). The two compounds showed in addition two dd signals at δ 6.16 and 6.11 ppm, respectively, characteristic for the NH protons



Scheme 3

(H-7), and two doublets at δ 10.26 and δ 10.12 ppm, respectively, characteristic for NH protons (H-8). When the protons H-7 and H-8 were exchanged with D_2O the methine protons (H-6) of compounds **20a, b** appeared as two singlets at almost the same δ value.

Analysis of the COSY spectrum of **20b** provides additional evidence for the suggested structure. Thus, the low field signal at δ 6.66 (d, $J_{6,7}$ = 3.7 Hz, 1H) and that at δ 6.16 ppm (dd, $J_{7,8}$ = 6.0 Hz, $J_{6,7}$ = 3.8 Hz, 1H) are mutually correlated. Moreover, the signal at δ 6.16 showed additional correlation with the doublet signal at δ 10.12 ppm (d, $J_{7,8}$ = 6.0 Hz, 1H), and also the ^{13}C NMR spectrum of compound **20b** displayed characteristic signals at δ 63.54 characteristic for the sp^3 CH-carbon (C-6).

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

References: 29

Schemes: 4

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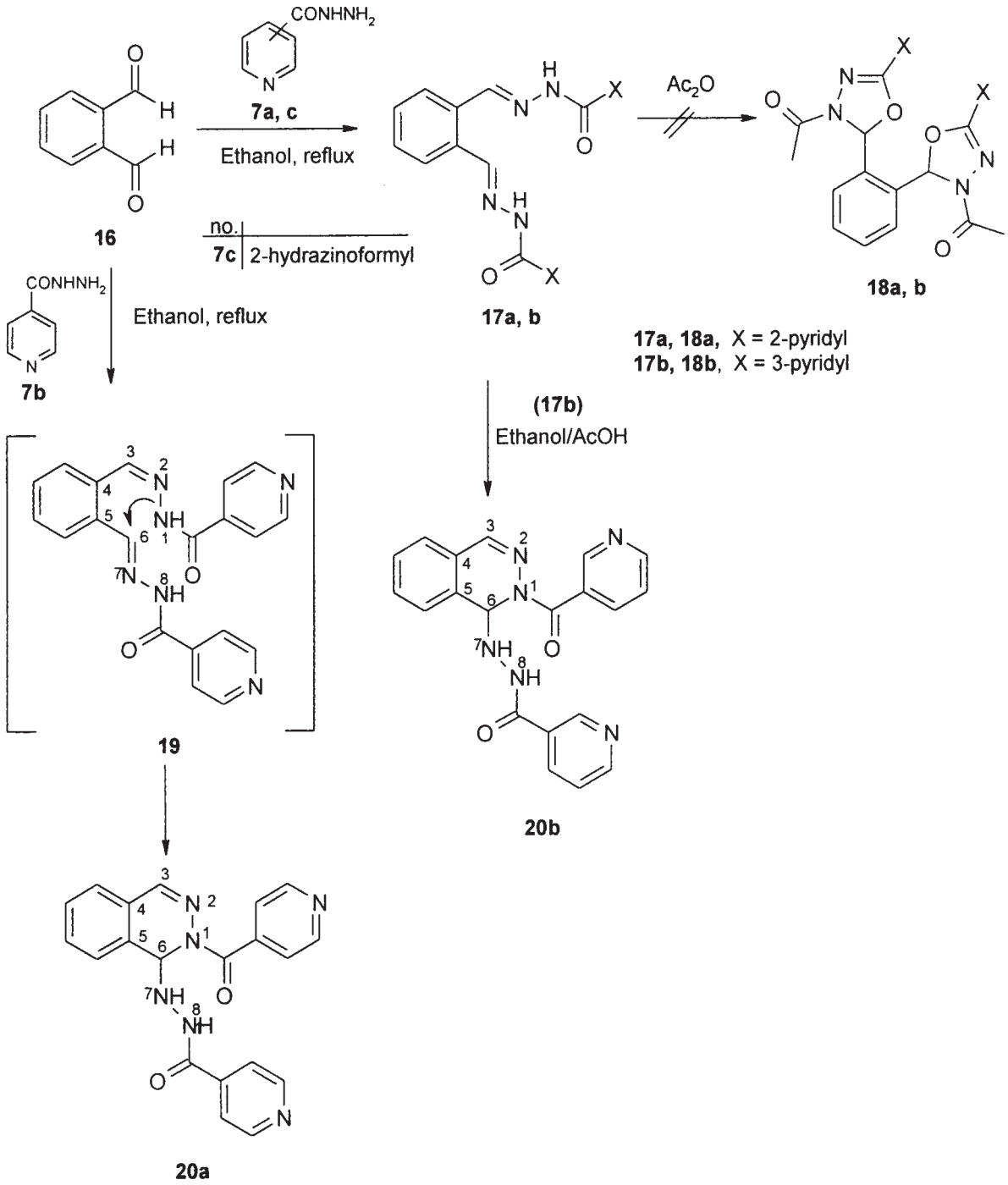

Scheme 4

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