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## 2-Arylhydrazononitriles as building blocks in heterocyclic synthesis: A novel route to 2-substituted-1,2,3-triazoles and 1,2,3-triazolo[4,5-*b*]pyridines

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Published: 13 March 2007

Received: 11 November 2006

Beilstein Journal of Organic Chemistry 2007, 3:12 doi:10.1186/1860-5397-3-12

Accepted: 13 March 2007

This article is available from: <http://bjoc.beilstein-journals.org/content/3/1/12>

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### Abstract

2-Arylhydrazono-3-oxobutanenitriles **2** was reacted with hydroxylamine hydrochloride to yield amidooxime **3**. This was cyclized into the corresponding oxadiazole **4** on refluxing in acetic anhydride. When refluxed in DMF in presence of piperidine, the corresponding 1,2,3-triazoleamine **5** was formed. The latter was acylated to **6** by addition of acetic anhydride while treatment of **5** with malononitrile gave the 1,2,3-triazolo [4,5-*b*]pyridine **8**. Treatment of acetyl derivative **6** with DMFDMA gave enaminone **9**. The enaminone **9** was coupled with benzenediazonium chloride to yield phenylazo-1,2,3-triazolo [4,5-*b*]pyridine **10**. Trials to convert compound **14** into 1,2,3-triazolo [4,5-*d*]pyrimidine **15** via refluxing in AcOH/NH<sub>4</sub>OAc failed. Instead the hydrolyzed product **5** was formed.

### Introduction

Interest in 1,2,3-triazole chemistry has recently been revived. [1-4] Zaprinst (1) is used as cyclic AMP phosphodiesterase inhibitor. [5] Plenty of 1,2,3-triazoles have also been reported to have useful pharmaceutical potential. [6-9] Synthetic approaches to 1,2,3-triazoloazines are rather limited. There are in fact few known routes to 4-functionally substituted 1,2,3-triazole-5-amines. [7] The latter is one of the logical starting points for condensed 1,2,3-triazoloazines. In the present article we provide a versatile route to these derivatives.

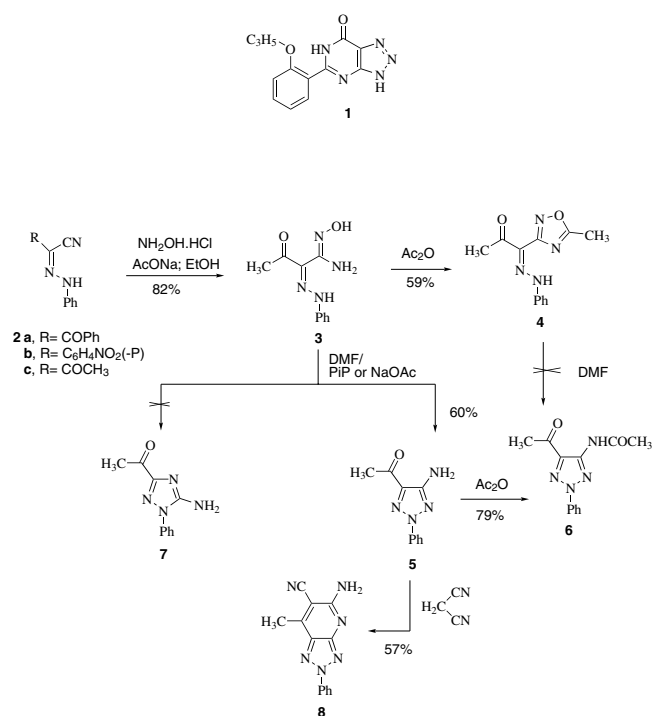
### Results and discussion

Elnagdi *et al* [10] have reported that arylhydrazononitriles reacted with hydroxylamine hydrochloride in ethanolic sodium acetate yielded amidooxime **3** that cyclized into

aminoisoxazoles on treatment with mineral acids. Moreover, recently it was shown that refluxing **2a** with hydroxylamine hydrochloride in DMF/piperidine afforded 1,2,3-triazoles whose structure was established by X-ray crystal structure. [11] On the other hand reacting **2b** with hydroxylamine hydrochloride in DMF/piperidine afforded 5-amino-1,2,4-triazole via a rare Tiemann-like rearrangement. In order to clarify the rule of the substituent and the reaction condition we have investigated the behavior of compound **2c** with hydroxylamine hydrochloride in DMF/piperidine.

Reacting **2c** with hydroxylamine hydrochloride in ethanolic sodium acetate afforded the corresponding amidooxime **3** in good yield. Formation of amidooximes on reacting 2-arylhazdononitriles with hydroxylamine

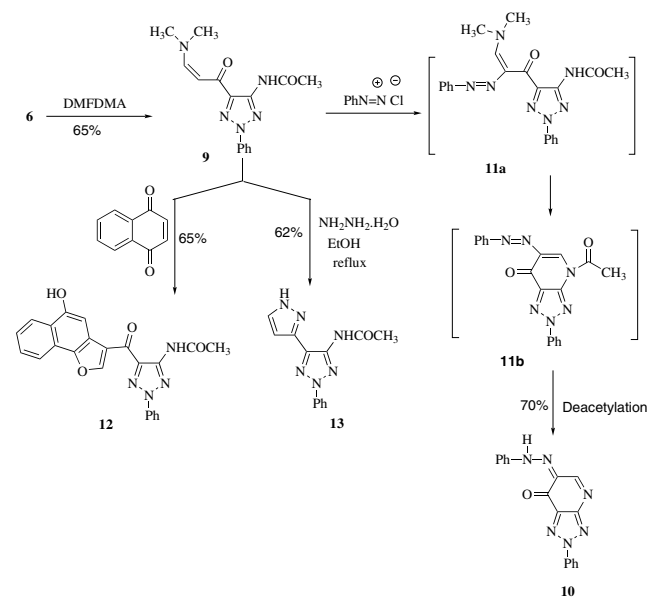
hydrochloride under similar conditions has been reported earlier by Elnagdi *et al.* [10,11] Attempted cyclization of **3** into 1,2,3-triazole *via* reflux in acetic anhydride, as has been reported recently, [11] afforded a product that can be assigned as 1,2,4-oxadiazolylphenylhydrazone structure **4** or the isomeric acetylamino-1,2,3-triazole structure **6**. Phenylhydrazono-1,2,4-oxadiazoles have been reported to rearrange thermally into acylamino-1,2,3-triazoles. [12] Compound **5** could be obtained *via* refluxing **3** in DMF in the presence of piperidine or anhydrous sodium acetate. Acylation of the latter afforded the acetylamino-1,2,3-triazole **6** which proved to be different in all respects from **4**. To exclude the possible rearrangement of **3** prior to cyclization (Tiemann rearrangement), [13] as has been noted recently by Al-Matar *et al.*, [14] and the possibility that the really formed product is the 5-amino-1,2,4-triazole **7**. We decided to investigate further the chemical reactivity pattern of the cyclized product (Scheme 1) to support our conclusion.



**Scheme 1: Synthesis of triazolopyridine 8.**

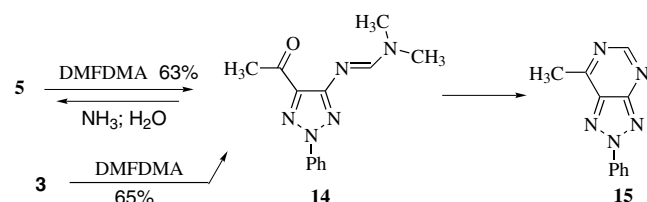
Compound **5** was reacted with malononitrile in refluxing DMF to yield the triazolopyridine **8**, thus confirming that the aminofunction and the acetyl function are adjacent. Moreover, reacting **6** with dimethylformamide dimethyl-acetal (DMFDMA) afforded the *cis* enaminone **9** ( $J = 8$  Hz) despite the fact that secondary enaminones have been established to prefer adopting the *trans* configuration. [15] Compound **9** was coupled with benzenediazonium chloride most likely through the intermediate **11a**. The latter intermediate cyclized into **11b**. Deacetylation of

**11b** followed by hydrogen shift produced **10**. This again confirms that the acetyl and the amino functions in cyclization product are adjacent as in **5** and therefore excluding **7** (Scheme 2). Typical of enaminones, compound **9** reacts with naphthoquinone to yield the benzofuran **12** and with hydrazine hydrate to yield pyrazolyl-1,2,3-triazole **13** in good yields.



**Scheme 2: Synthesis of 1,2,3-triazoles and 1,2,3-triazolo[4,5-b]pyridines.**

Attempts to convert **4** into oxadiazolylhydrazone **6** by heating in DMF afforded **14** whose structure could be elucidated through synthesis independently from **3**. Trials to cyclise **14** into triazolopyrimidine **15** failed under a variety of conditions. It is thought that compound **15**, if formed, has hydrolyzed to **5** (Scheme 3).



**Scheme 3: Identification of 1,2,3-triazole 14.**

## Conclusion

An excellent simple route to 2-substituted-1,2,3-triazols has been reached. It could be also revealed that the formed triazoles are excellent precursors to condensed triazoles and azolytriazoles.

## Experimental Section

[See Additional File 1]

## Additional material

### Additional File 1

Experimental Section. the experimental data and the results of analysis  
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## Acknowledgements

The authors are grateful to Professor M. H. Elnagdi from Cairo University for interest and discussion. Also the authors are grateful to Kuwait University, Research Administration for financial support through project No. SC11/02 and for SAF facilities project Gs01/02; Gs03/01.

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