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Regioselective addition of Grignard reagents to 2,6-dicyanoanilines and cyclization to new quinazoline derivatives under thermal/microwave irradiation conditions☆

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Abstract

Two strategies have been developed for the synthesis of novel quinazoline derivatives. 2,6-Dicyanoanilines were reacted with Grignard reagents followed by cyclization to give two quinazoline regioisomers **2** and **3**. Alternately 2,6-dicyanoanilines on reaction with Grignard reagents gave imine regioisomers **4** and **5**. Each imine regioisomer was separated and independently cyclized to give new quinazoline derivatives **6**, **7** and **8**, **9**, respectively, under different microwave irradiation conditions.

Keywords: 2,6-Dicyanoanilines; Regioisomers; Quinazolines; Grignard reagents

1. Introduction

The quinazoline nucleus features in many alkaloids and is known to show a wide range of biological activity [1]. A few non-classical quinazoline analogues of folic acid have remarkable antibacterial and antimalarial effects and most prominent is trimetrexate [2]. It is also considered as an anticancer agent and has similar levels of inhibitory potency as methotrexate towards dihydrofolate reductase (DHFR). Prazosin, a quinazoline-based drug, is used as an antihypertensive agent [3]. The prime requirement for any organic molecule to act as a potential drug is low dosage, low toxicity and effective binding to the specific disease causing receptor site with high solubility. In order to target the requirements, specific substituents at appropriate positions of a molecule are desirable. One such group is fluorine [4] or trifluoromethyl [5,6] which, at a strategic position in the molecule, alters the properties of molecule by promoting activity due to high lipid solubility. Previous syntheses of quinazolines are mainly from *o*-aminoketones [7], *o*-aminonitriles [8], enamines via aza Wittig reaction [9], electrocyclic ring closures [10,11] and 1,3-dimethoxybenzenes [12].

Based on the importance of quinazoline derivatives and our continued interest in fluorinated molecules [13], we have selected 2,6-dicyanoanilines (**1**) [14,15], interesting trifunctional intermediates and subjected them to Grignard addition in two ways. One way was addition of Grignard reagents followed by cyclization in a single step to quinazoline derivatives (**2** and **3**). Another way was addition of Grignard reagents to compounds **1** to give imine regioisomers (**4** and **5**). Then, each isomer was separated and independently cyclized to quinazolines **6**, **7** and **8**, **9**, respectively, under microwave irradiation conditions.

2. Results and discussion

Unsymmetrical 2,6-dicyanoanilines (**1**) were reacted with various Grignard reagents and the resulted reaction mixture was treated with trifluoroacetic/acetic anhydrides in situ to give quinazoline regioisomers (**2** and **3**) in different proportions. The yields were in the range 60–70%. The main reaction is addition of Grignard reagents to the less hindered nitrile (CN) carbon in preference to highly hindered and followed by cyclization in presence of trifluoroacetic/acetic anhydride resulted two

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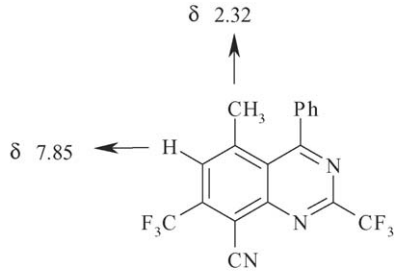
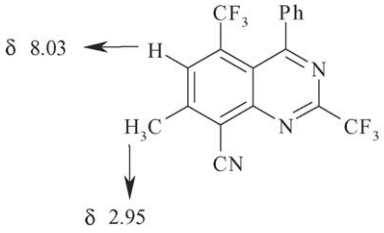
quinazoline regioisomers, as one isomer in major and another isomer in minor depending upon the substituents used. The role of substituents on reaction time, yield and ratio of products formed was established. Thus, the methyl substituent in compound **1** promotes formation of product **2** as the major, whereas the phenyl substituent reverses the formation of products. Regioselectivity is high with phenyl substitution in compound **1** and also in the Grignard reagents. The reaction is schematically drawn in Scheme 1.

The regioisomers **2** and **3** were separated and identified based on characteristic differences in their ^{1}H NMR spectra. In a specific example of **2a** and **3a**, we observed a change in chemical shift of CH_3 and C–H proton on C-6 carbon. In **3a** the methyl group as well as C–H proton on C-6 carbon appeared downfield with reference to **2a**. It is attributed to the ortho nitrile (CN) effect on the methyl group and the ortho CF_3 group effect on the C-6 proton in line with C-4 phenyl group as a result appeared in downfield in comparison to **2a** isomer. Similar trend is followed in other isomers. The products synthesised are tabulated in Table 1.



2a



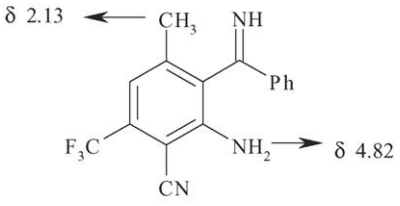
3a

The reaction of compound **1** with Grignard reagents followed by aryl aldehydes is further extended in order to obtain 2-arylsubstituted quinazolines; however, in all the cases imine derivatives (**4** and **5**) are exclusively formed. Thus, unsymmetrical 2,6-dicyanoanilines (**1**) on reaction with Grignard reagents gave two imine regioisomers (**4** and **5**). The reaction trend is similar to the first strategy and obtained one of the isomer major and another minor. The regioisomers are with close polarity, separated by column and identified based on spectral data (Scheme 2).

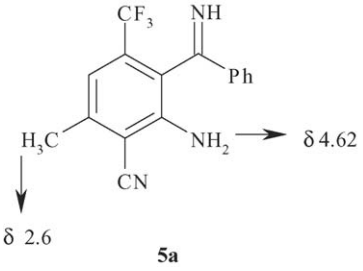
Table 1
Quinazoline regioisomers

Entry	Product	R	R′	R″	Ratio (%)	Yield (%)
1	**2a**	CH_3	Ph	CF_3	65	42
	3a	CH_3	Ph	CF_3	35	22
2	**2b**	Ph	Ph	CF_3	28	22
	3b	Ph	Ph	CF_3	72	56
3	**2c**	Ph	Ph	CH_3	25	15
	3c	Ph	Ph	CH_3	75	46
4	**2d**	Ph	C_2H_5	CF_3	40	23
	3d	Ph	C_2H_5	CF_3	60	35

The ^{1}H NMR spectra of two regioisomers (**4a** and **5a**) show characteristic differences in the chemical shift of CH_3 and NH_2 signals of one isomer to other isomer are varied due to electronic factors. It depends on mainly two groups, i.e., CF_3 and CN. If CF_3 and CN are para to each other, the NH_2 signal appears more upfield. Similarly, the CH_3 signal when it is ortho to CN appeared downfield as in compound **3a** and para to nitrile appeared in upfield. It is presumed that the ortho nitrile has more influence on CH_3 than para and as a result the signals for CH_3 group appeared in downfield and upfield, respectively (Table 2).



4a



5a

In a typical reaction, one of the compounds **4a** was reacted with benzaldehyde in acetic acid under thermal conditions at 110 °C for 4 h to give a number of products. As a result mixture of products **6** and **7** formed in a low yield of 35%. As an alternate method, the same reaction of **4a** with benzaldehyde was conducted under microwave irradiation conditions with 300 W power in 4 min, to give exclusively 1,2-dihydroquinazolines **6a** and no further reaction even at longer time and higher concentration of aldehyde. In contrast with 450 W power of microwave irradiation, quinazoline **7a** was obtained directly. Quinazoline was identified based on spectral data and confirmed by single crystal X-ray analysis (Fig. 1).

Thus, all four compounds **4**–**5** were independently reacted with various aldehydes under two sets of microwave irradiation conditions to obtain 1,2-dihydroquinazolines (**6** and **8**) and quinazolines (**7** and **9**). Thus, the reaction using 300 W microwave irradiation gave exclusively compounds **6** and **8**, whereas with 450 W microwave irradiation gave compounds **7** and **9**. The reaction involved formation of Schiff's base