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Synthetic strategies to prepare 2-alkyl, 2-aryl and 2-acetylenyl substituted 4,6-diamino-1,3,5-triazines

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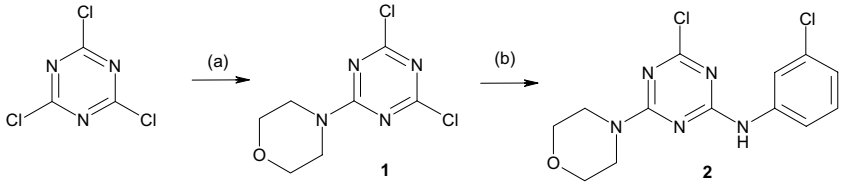
Abstract—We have developed synthetic protocols to generate 2-alkyl, 2-aryl and 2-acetylenyl substituted 4,6-diamino-1,3,5-triazines from the corresponding 2-chloro compound.

The triazine scaffold is found in compounds presenting a wide spectrum of biological activity. This core has been utilised in diverse pharmaceutical applications such as antiproliferative, antitubulin, antiangiogenic and antidepressive agents or in plant-protection applications such as the triazine herbicides.[1] Other factors which have contributed to the widespread use of triazine libraries in drug discovery are the ease of manipulation and the availability of cheap starting materials used to build this class of compounds.

In an anticancer project aiming to identify PI3 kinase pathway inhibitors by monitoring FOXO1 translocation, a member of the Forkhead family of transcription factors,[2] we screened a library of 265,000 commercial compounds using a cell based FOXO1 Redistribution® assay.[3] The screening campaign provided the substituted triazine **2** as a 3 μM hit.

Trisubstituted 1,3,5-triazine derivatives can be generated by stepwise replacement of the chlorine atoms of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) by amines, alcohols or thiols. This strategy takes advantage of the decrease in reactivity after introduction of each substituent. Derivatives containing three different substituents are obtained in a reasonable yield and purity.[4] The scaffold is therefore well suited for combinatorial library generation and solution phase[4,5] or solid phase libraries[1b,c,6] have been reported.

Diverse methods for the introduction of alkyl substituents on cyanuric chloride are described in the literature,



Scheme 1. Reagents and conditions: (a) acetone, K_2CO_3, morpholine, 0 °C, 83% and (b) acetone–water (5:1), 3-chloroaniline, K_2CO_3, 40 °C, 94%.

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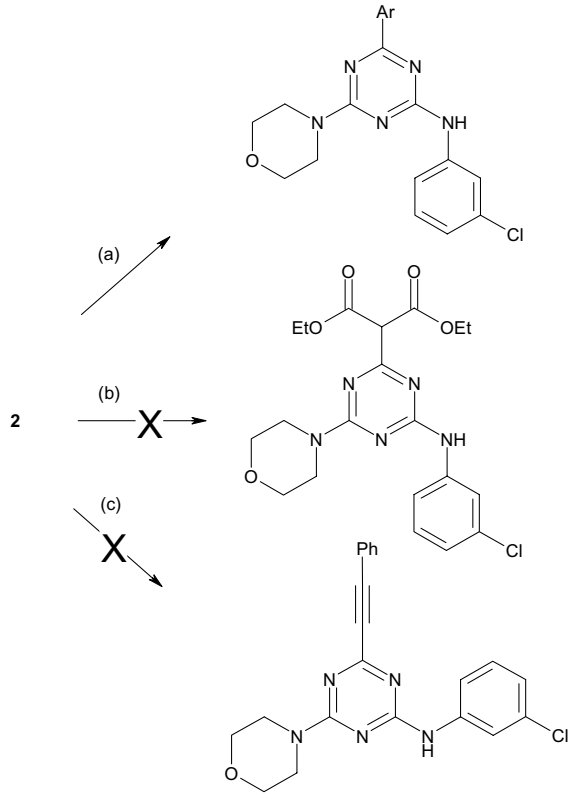


Scheme 2. Reagents and conditions: (a) DME, $Pd(PPh_3)_4$, K_2CO_3 (2 M), $ArB(OH)_2$, 80 °C, 3 days (Ar (yield) = phenyl (62%), 2-thienyl (44%), 3-furyl (55%), 3,4-dimethoxy (37%)); (b) THF or DMF, diethyl malonate, NaH, room temperature to 60 °C, 14 h; only starting material recovered and (c) toluene, DIPEA, CuI, $Pd(PPh_3)_4$, PhC≡CH or PhC≡CMgBr, Et_2O, 0 °C to room temperature or 100 °C; only starting material recovered.

such as palladium mediated coupling of organozinc or organotin reagents,[7] addition of Grignard reagents[8] and addition of silyl enol ethers.[9]

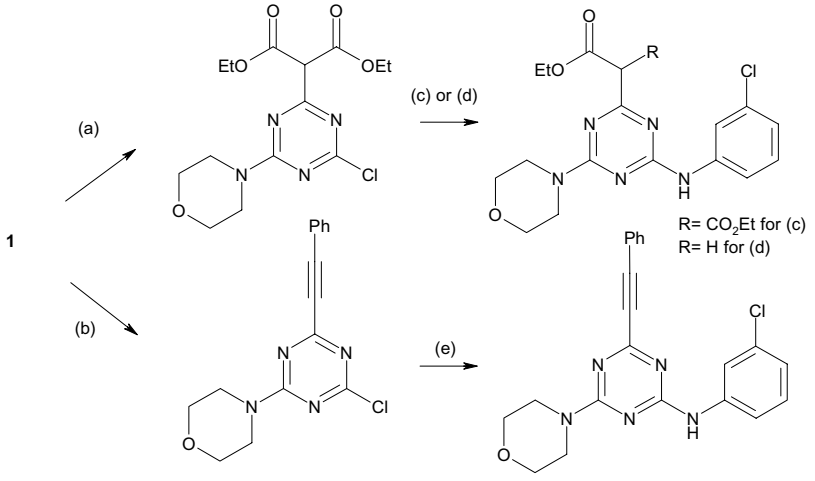
In order to establish a structure activity relationship at the chlorine-substituted position on the triazine ring of compound **2** we set out to prepare a selection of analogues replacing the chlorine atom with malonyl, aryl or alkynyl substituents.

The original hit **2** was prepared, on a 20 g scale, via two consecutive S_NAr reactions, first reacting morpholine with cyanuric chloride followed by addition of 3-chloroaniline, in 78% overall yield (Scheme 1).

With compound **2** in hand, we investigated the replacement of the final chlorine (Scheme 2). Aryl substituents were successfully introduced by Suzuki and Miyaura[10] coupling using the methodology developed by Cooke et al.[11] (Scheme 2a).

To our knowledge the use of a malonate derivative as a soft nucleophile has not yet been described for either cyanuric chloride or dichlorotriazines. The malonate moiety also constitutes an advantageous handle for further elaborations. However, introduction of malonate on compound **2** proved unfruitful (Scheme 2b). We believe that this may be due to the malonate nucleophile acting as a base and deprotonating the aniline nitrogen on compound **2**. The increased electron density on the triazine ring resulting from this deprotonation would then prevent any addition from taking place.

To overcome this problem, we instead investigated the malonate addition on 2,4-dichloro-6-morpholin-4-yl-1,3,5-triazine **1**. This change in order of addition now allowed the successful introduction of the malonate group to the triazine core (Scheme 3a). When 3-chloroaniline was introduced in the final step under basic conditions (Scheme 3c) the diester product was isolated. Alternatively when the reaction was carried out under acidic conditions (Scheme 3d) further decarboxylation was observed and the mono ester was isolated as the main product.



Scheme 3. Reagents and conditions: (a) THF, diethyl malonate (1.2 equiv), NaH (4 equiv), 0 °C to room temperature, 25%; (b) toluene, DIPEA, CuI, $Pd(PPh_3)_4$, PhC≡CH, room temperature, 48 h, 71%; (c) THF, K_2CO_3, 3-chloroaniline, 14%; (d) MeCN, TFA (2 equiv), 3-chloroaniline, 80 °C, sealed tube, 18% and (e) THF, K_2CO_3, 3-chloroaniline, 33%.

The functionalisation of triazines by alkynes has been described using Sonogashira coupling[12,13] or Grignard[14] addition methodologies on 2-chloro-4,6-dimethoxy-1,3,5-triazine. In our case, the Sonogashira coupling failed to give any product when carried out on compound **2** or cyanuric chloride (Scheme 2c).

Using a similar strategy as described for the malonate derivative, the coupling reaction with 2,4-dichloro-6-morpholin-4-yl-1,3,5-triazine **1** afforded the alkyne derivative in good yield (Scheme 3b). The final displacement was achieved under basic conditions with 3-chloroaniline (Scheme 3e).

In conclusion, we have prepared a series of trisubstituted triazines where one of the positions contains a carbon substituent. In our hands, the order of synthetic steps depends on the nature of the substituent. Whereas aryl groups could be introduced during the last step via Suzuki coupling on compound **2**, introduction of the malonyl and acetylenyl moieties is necessary at an earlier stage on the dichlorotriazine **1**, followed by the final introduction of the aniline.

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