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Terminal alkyne-functionalized triazine by Sonogashira coupling: synthesis of a potential cell signalling inhibitor via click chemistry

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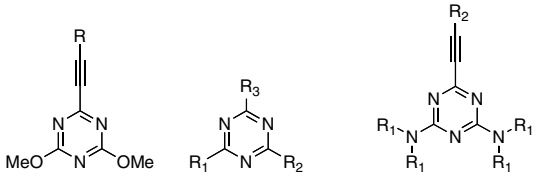
ABSTRACT

Introduction of the acetylene group on the 1,3,5-triazine scaffold was studied under various conditions. We describe here a new method to functionalize a triazine ring using Sonogashira coupling between 2-benzylsulfanyl-4,6-dichloro-1,3,5-triazine and trimethylsilylacetylene to give the corresponding 2-benzylsulfanyl-4-chloro-6-(trimethylsilyl)ethynyl-1,3,5-triazine. The latter was then used to obtain phosphoric acid mono-{4-[4-(4-amino-6-benzylsulfanyl-1,3,5-triazin-2-yl)-1,2,3-triazol-1-yl]-phenyl} ester via click chemistry by Huisgen 1,3-dipolar cycloaddition reaction.

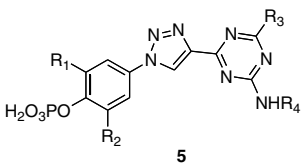
1,2,3-Triazoles have gained increasing attention in medicinal chemistry[1] since the introduction of the so-called 'click chemistry' or Cu(I)-catalyzed 1,3-dipolar alkyne-azide coupling reaction, which was pioneered by Sharpless.[2] Protein tyrosine phosphatases (PTPs) and protein tyrosine kinases (PTKs) have been the focus of considerable drug discovery efforts in recent years, owing to their implication in regulating cell-signalling pathways. In this context, application of click chemistry recently led to the synthesis of libraries of PTP inhibitors,[3] and to the synthesis of the growth factor receptor-bound protein 2 (Grb2) SH2 domain-binding inhibitors designed to antagonize or modulate PTK signalling,[4] in addition to classical rational design of such inhibitors.[5]

Exploiting the triazine privileged structure[6,7] in medicinal chemistry[8] via click chemistry, which enables the construction of libraries with asymmetric diversity, would be of great interest. Alkynylation of 1,3,5-triazine derivatives has been reported under various conditions. Menicagli and Samaritani[9] described the synthesis of 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines **1** by Sonogashira cross-coupling between alk-1-ynes and 2-chloro-4,6-dimethoxy-1,3,5-triazine **2** in the presence of different palladium catalyst systems (Fig. 1). Furthermore, Grignard alkynylation of 2,4,6-trichloro-1,3,5-triazine **3** (cyanuric chloride) was revisited,[10] allowing access to 2-(alk-1′-ynyl)-4,6-dialkylamino-1,3,5-triazines **4**. Importantly, it appears that none of these papers mention the synthesis of triazines possessing the terminal acetylene group, required in our case for the Huisgen 1,3-dipolar cycloaddition reaction. To our knowledge, the introduction of this functionality, via Grignard alkynylation from cyanuric chloride **3**, was only reported in a patent in 1972.[11]



1 R = alkyl **2** $R_1 = R_2 = OMe$, $R_3 = Cl$ **3** $R_1 = R_2 = R_3 = Cl$ **4** R_2 = alkyl, Ph

Figure 1. Alkynylation of 1,3,5-triazine derivatives.



5

Figure 2. Triazine-functionalized, 1,4-disubstituted-1,2,3-triazoles **5**.

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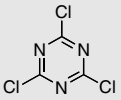
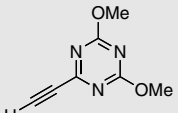
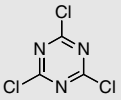
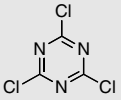
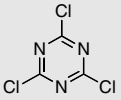
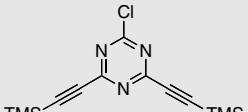
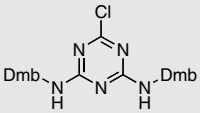
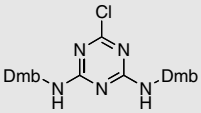
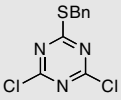
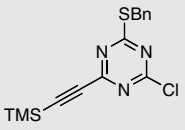
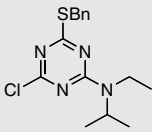
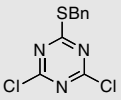
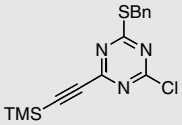
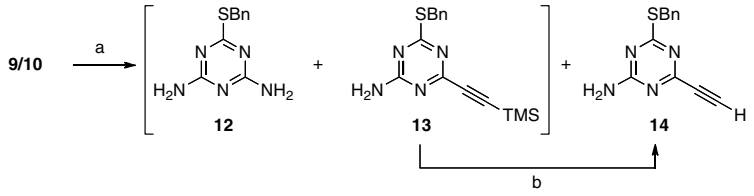
Thus, we have designed phosphate-containing 1,4-disubstituted-1,2,3-triazoles **5** as potential cell signalling inhibitors[3,12] using click chemistry strategy (Fig. 2). Herein, we present the preliminary results of our investigation on the introduction of the ethynyl functionality on substituted 1,3,5-triazine derivatives, and the synthesis of phosphoric acid mono-{4-[4-(4-amino-6-benzylsulfanyl-1,3,5-triazin-2-yl)-1,2,3-triazol-1-yl]-phenyl} ester **5** ($R_1 = R_2 = H$, $R_3 = SBn$, $R_4 = H$) via click chemistry.

The introduction of the terminal acetylene functionality from **3** was demonstrated[11] using [(trimethylsilyl)ethynyl]magnesium bromide prepared from trimethylsilylacetylene (TMSA) and ethylmagnesium bromide (Table 1, entry 1). Addition of MeOH to the

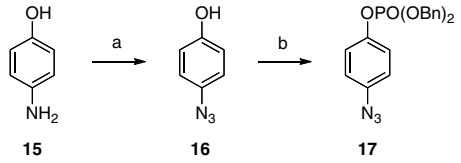
Table 1
Introduction of the trimethysilylethynyl group on substituted 1,3,5-triazine derivatives[a]

Entry	Reaction conditions	Starting material triazine	Product yield[b] %
1	1. HC≡C–TMS, EtMgBr THF, then addition of MeOH 2. Hydrolysis	 **3**	 **6**[11]
2	HC≡C–MgBr (1 equiv) THF, 0 °C, then addition of MeONa	 **3**	Decomposition
3[c]	HC≡C–MgBr (1 equiv) $Ni(acac)_2$, PPh_3, THF, 0 °C then addition of MeONa	 **3**	Decomposition
4	HC≡C–TMS (1 equiv) $PdCl_2(PPh_3)_2$, CuI, DIPEA THF, rt, 20 h	 **3**	 **7**[d] 46%
5	HC≡C–TMS (1.5 equiv) Pd/C, PPh_3, CuI, DIPEA MeCN, 80 °C, 20 h, sealed tube	 **8**	No reaction
6	HC≡C–TMS (1.5 or 3 equiv) Pd/C, PPh_3, CuI, K_2CO_3, MeCN, 80 °C, 20 h, sealed tube	 **8**	No reaction
7[e]	HC≡C–TMS (1.5 equiv) Pd/C, PPh_3, CuI, DIPEA MeCN, 80 °C, 24 h, sealed tube	 **9**	 **10** 15%  **11** 25%
8[f]	HC≡C–TMS (2 equiv) $PdCl_2(PPh_3)_2$, CuI, DIPEA THF, rt, 20 h	 **9**	 **10** 38%

[a] Unless otherwise specified, reactions were carried out with Pd catalyst 0.04 equiv, CuI 0.04 equiv, PPh_3 0.16 equiv, base 2.5 equiv.
[b] Yields were determined by ^1H NMR analysis unless otherwise stated.
[c] $Ni(acac)_2$ 0.01 equiv, PPh_3 0.02 equiv.
[d] Isolated yield.
[e] Flash chromatography of the crude product gave two fractions: 4-benzylsulfanyl-6-chloro-*N*-ethyl-*N*-isopropyl-1,3,5-triazin-2-amine **11** (25%) and an inseparable mixture of the starting material **9** and the desired cross-coupling product **10** (15%).
[f] Scaled-up reaction (8 g of **9**), **10** was inseparable from the starting triazine after flash chromatography.



Scheme 1. Synthesis of alkyne **14**. Reagents and conditions: (a) NH_3 (g), THF, rt, 20 h; (b) K_2CO_3, MeOH/THF (1:1), rt, 2 days, 80% (combined yield).



Scheme 2. Synthesis of (4-azidophenyl)dibenzylphosphate **17**. Reagents and conditions: (a) 4-aminophenol **15** diluted in HCl aq (0.5 M HCl), 0 °C, then addition of $NaNO_2$ aq (1.5 equiv), 0 °C, then addition of NaN_3 aq (1.5 equiv), 0 °C (dilution in order to obtain a 0.2 M HCl final solution), 20 h, 89%; (b) $(BnO)_2P(O)H$ (2.5 equiv), DIPEA (5 equiv), DMAP (0.5 equiv), CCl_4/CH_3CN (1:5), −15 °C, 3 h, 81%.

resulting alkynylated product followed by cleavage of the TMS protecting group led to 2-ethynyl-4,6-dimethoxy-1,3,5-triazine **6**. By contrast, treatment of **3** with ethynylmagnesium bromide only resulted in decomposition of the starting material (entry 2). An identical outcome was observed when Grignard alkynylation was attempted with the $Ni(acac)_2$-PPh_3 system[13] (entry 3). Next, we examined the Sonogashira reaction[14] of **3** with TMSA in the presence of $PdCl_2(PPh_3)_2$ which gave 2-chloro-4,6-bis[(trimethylsilyl)ethynyl]-1,3,5-triazine **7** in 46% yield, with only traces of the required monoethynylated product (entry 4). We then envisioned the Sonogashira coupling of 6-chloro-N^2,N^4-bis(2,4-dimethoxybenzyl)-1,3,5-triazine-2,4-diamine **8**—bearing two acid-labile dimethoxybenzyl (Dmb) protecting groups for the amines[15]—and TMSA. Note that this triazine scaffold could lead to the synthesis of triazoles **5** featuring two nitrogen functionalizations at C4 (NHR_4) and C6 (R_3). Unfortunately, with (Pd/C)/PPh_3/CuI as the catalytic system,[9] no reactions occurred (entries 5 and 6). Finally, we opted for 2-benzylsulfanyl-4,6-dichloro-1,3,5-triazine **9**[16] as the substrate, which allowed an orthogonal synthetic strategy, via the sulfone chemistry (i.e., oxidative activation of the thioether), for the generation of 1,3,5-trisubstituted combinatorial triazine libraries.[16] Under the previous reaction conditions with *N*,*N*′-diisopropylethylamine (DIPEA) as a base, triazine **9** gave rise to the formation of the desired 2-benzylsulfanyl-4-chloro-6-(trimethylsilyl)ethynyl-1,3,5-triazine **10** in 15% yield, accompanied with 25% yield of 4-benzylsulfanyl-6-chloro-*N*-ethyl-*N*-isopropyl-1,3,5-triazin-2-amine **11** (entry 7). The latter results from the amination of the starting material by DIPEA followed by the elimination of an isopropyl group.[9b] The same coupling reaction conducted at 25 °C for 24 h led to the recovery of triazine **9**. However, replacement of the catalyst (Pd/C)/PPh_3 by $PdCl_2(PPh_3)_2$ afforded the desired cross-coupling product **10** in a synthetically useful 38% yield (entry 8).

The required deprotection of trimethylsilylacetylene **10** existing as a mixture with **9** was problematic, since the reaction under TBAF conditions (TBAF, THF, rt) resulted in decomposition, and that the treatment of **10** with potassium carbonate (K_2CO_3, MeOH/THF, rt) not only yielded to the expected free acetylene group but also to concomitant substitution by methoxide anion on the 6-Cl position. We overcame this difficulty by a prior introduction of the required NH_2 group from the mixture containing 2-benzylsulfanyl-4,6-dichloro-1,3,5-triazine **9** and alkyne **10** (Scheme 1): thus, reaction of ammonia with this mixture led to two fractions after flash chromatography, the less polar as an inseparable mixture of **12** and **13** (60% yield as determined by ^1H NMR), and the more polar as pure isolated compound **14** (20%). Treating the mixture of **12** and **13** with K_2CO_3 allowed the quantitative transformation of **13** into **14**, in a combined yield of 80%.

With compound **14** in hand, we next turned out our attention to the preparation of the desired 1,4-disubstituted-1,2,3-triazole **5**.[17,18] First, (4-azidophenyl)dibenzylphosphate **17**[19] was prepared in an optimized two-step process. 4-Azidophenol **16** was obtained from 4-aminophenol by diazotization followed by treatment of the resulting diazonium salt with azide anion (89%). Phosphorylation of **16** with dibenzylchlorophosphate[20] (in situ prepared from dibenzylphosphite) gave **17** in 81% yield (Scheme 2).

Finally, the 1,3-dipolar Huisgen cycloaddition of alkyne **14** and aryl azide **17** was carried out to give triazole **18** in 54% yield (Scheme 3). Deprotection of **18** led to triazinyl-triazole phosphate **5** (66%) which was purified by reversed-phase C18 chromatography (CH_3CN/H_2O).

In conclusion, we described a study on the introduction of the ethynyl group on substituted 1,3,5-triazine derivatives via Sonogashira coupling. To the best of our knowledge, triazole **5** is the first example of click chemistry by Huisgen cycloaddition reaction applied to the privileged structure triazine.[21] This method will be optimized and used in the synthesis of triazine libraries. This compound and analogues will be investigated as potential cell signalling inhibitors.

Acknowledgments

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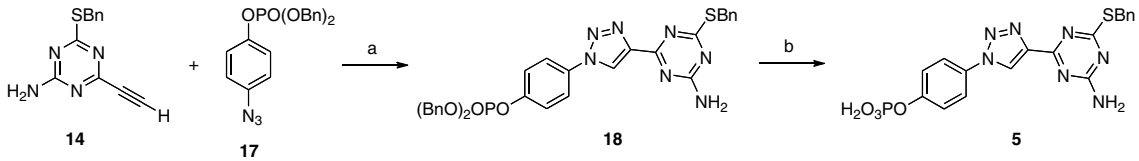

Scheme 3. Synthesis of triazinyl-triazole phosphate **5**. Reagents and conditions: (a) ascorbic acid (0.1 equiv), $CuSO_4$ (0.01 equiv), H_2O/*t*-BuOH (1:1), 30 °C, 24 h, 54%; (b) TFA 95%, rt, 2 h, 66%.

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