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First Cross-Coupling Reactions on Tetrazines

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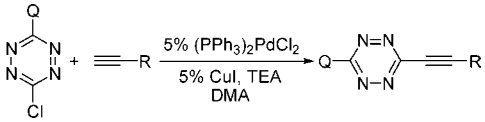
ABSTRACT



A series of substituted chlorotetrazines were reacted with different terminal alkynes under Sonogashira or Negishi coupling conditions to furnish alkynyl-tetrazines in good to moderate yield. The electron-donating properties of the substituent on the tetrazine core were found to have a significant influence on the success of the reaction. These results constitute the first cross-coupling reactions on tetrazines.

The chemistry of tetrazines has gained increased attention in the last few decades,[1] due mostly to their applications in organic synthesis,[2] crop protection,[3] and pyrotechnics.[4] Their basic structural feature, the electron-deficient heterocyclic core, is the key to their most extensively utilized transformation, the "inverse electron-demand" Diels−Alder reaction, that provides an attractive route to pyridazines.[5] A major limitation, however, is the relatively small number of nonsymmetrically substituted tetrazines due to the difficulty of their preparation. The problematic step of their synthesis is usually the formation of the tetrazine core from the appropriately substituted carboxylic acid derivatives, which is hindered by low yield and a difficult separation procedure. Alternative approaches to nonsymmetrically substituted tetrazines, where greater selectivity and higher yields might be expected, include introduction of the desired moiety onto the tetrazine core by substitution or the chemical modification of one of the substituents on the ring.[6] The more frequently utilized nucleophilic substitution reactions have been mostly limited to amines and alcohols so far, providing selective substitution at the price of decreased cycloaddition ability,[7] due to the electron-donating nature of the new substituent. An obvious solution to this dilemma could be the use of carbon nucleophiles; however, there are only a limited number of publications in the literature[7d,8] describing such reactions, and they are also limited in terms of the nucleophile to the use of cyanides or malonic acid derivatives.

To overcome these difficulties we decided to use transition metal-catalyzed coupling reactions to attempt the introduction of carbon-based functional groups onto the tetrazine core. This approach, so far unprecedented in the literature, could open up the way for the preparation of a variety of new

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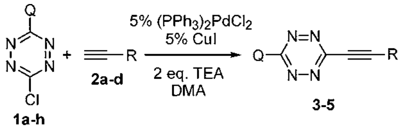
tetrazines but at the same time raises some questions as to the choice of the starting tetrazine derivative, coupling partner, catalyst, and reaction conditions, which can be all crucial to the success of the transformation.

The first point to address was the selection of the coupling partners. Due to the inherent lability of organometallic tetrazine derivatives,[9] we decided to use halotetrazines in our reactions. A survey of the literature revealed that only a limited number of bromotetrazines are known to date.[10] Chlorotetrazines on the other hand are more abundant, and utilizing the selective displacement of one chlorine atom of 3,6-dichlorotetrazine (**1h**)[4a] by different nucleophiles, we were able to obtain a series of 6-substituted 3-chlorotetrazines (**1a**−**e**,**g**).[3a,11]

As for the other coupling partner, reactive organometallic species such as organolithium or Grignard reagents[12] and arylzinc compounds[13] were ruled out, as they were found to react readily with the tetrazine core. Boronic acids also initiated unwanted side reactions under alkaline conditions,[14] and attempts to react **1a** with methyl acrylate under standard Heck conditions led only to decomposition. This directed our attention to alkynes as our choice of coupling partners, including four commercially available alkynes (**2a**−**d**).

In the first set of experiments, **1a** and **2a** were heated in various polar, non-nucleophilic solvents in an 80 °C oil bath in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (5 mol %), and TEA (2 equiv), and after the completion of the reaction (ca. 20 h) the coupling product **3a** was isolated in poor to acceptable yield. Of the solvents examined (DCM, THF, dioxane, DMF, DMA), DMA gave the best results. A screening of other ligands (dppf, dppe, P^tBu_3) using $Pd(OAc)_2$ as palladium source failed to give any significant improvement on the yield,[15] so our choice of conditions for the coupling experiments included heating in DMA in the presence of 5% of $Pd(PPh_3)_2Cl_2$, 5% CuI, and 2 equiv of TEA. The results of these experiments are summarized in Table 1.

Table 1. Sonogashira Coupling of Various Chlorotetrazines (**1a**−**f**) with Acetylene Derivatives **2a**−**d**



entry	Q	R	yield (%)[a]
1	morpholinyl (**1a**)	C(CH$_3$)$_2$OH (**2a**)	57 (**3a**)
2		Ph (**2b**)	56 (**3b**)
3		C4H9 (**2c**)	29 (**3c**)
4		TMS (**2d**)	dec
5	pyrrolidinyl (**1b**)	**2a**	52 (**4a**)
6		**2b**	23 (**4b**)
7		**2c**	56 (**4c**)
8	diethylamino (**1c**)	**2a**	30 (**5a**)
9		**2b**	48 (**5b**)
10		**2c**	65 (**5c**)
11	butylamino (**1d**)	**2c**	traces
12	amino (**1e**)	**2a**−**c**	starting material[b]
13	dimethylpyrazolyl (**1f**)	**2a**−**c**	dec[b]
14	methoxy (**1g**)	**2a**	dec[b]
15	chloro (**1h**)	**2a**	dec[b]

[a] Isolated yield of analytically pure product. [b] For details, see text.

6-Morpholino-chlorotetrazine (**1a**) reacted readily with 2-methyl-3-butyn-2-ol (**2a**), phenylacetylene (**2b**), and 1-hexyne (**2c**) and after the completion of the process gave the Sonogashira coupling products **3a**−**c** in varying yield. Parallel decomposition of the tetrazines and dimerization of the alkyne was also observed in each case. Attempts to extend the process to trimethylsilylacetylene (**2d**) were unsuccessful, as only decomposition was observed. The attachment of **2a** to the tetrazine core through its oxygen atom (nucleophilic substitution) was ruled out on the basis of the NMR and IR data. In the absence of the palladium catalyst, but retaining TEA and CuI, no product formation was observed, which excludes the formation of the products through nucleophilic substitution by an intermediate acetylide. The other tetrazines bearing a tertiary amine in the 6-position (**1b**,**c**) showed similar reactivity toward the alkynes **2a**−**c** and gave the ethynyltetrazines **4** and **5** in varying yield. The dimerization of the alkyne and decomposition of the tetrazines were observed in each case, the latter probably being responsible for the decreased yields. The sensitivity of the starting material is attributed to the electron-deficient nature of the heterocyclic ring, while the presence of two reactive moieties (tetrazine and acetylene) in the same molecule might lead to the decomposition of the coupling products. We were unable to detect the presence of any heterocyclic sideproduct in the reaction mixtures.

Further coupling experiments (entries 11−15) demonstrated that the reactivity of chlorotetrazines shows a marked dependence on the nature of the other substituent on the ring. Compounds bearing a secondary (**1d**) or primary amine (**1e**) scarcely reacted even after prolonged heating (24 h, 80 °C). The change of the catalyst to Fu's highly active $Pd-P^tBu_3$ system[16] did not lead to any improvement either, and the tetrazines remained unchanged. More electron-deficient chlorotetrazines (**1f**−**h**) on the other hand were extremely sensitive and led only to decomposition products. A survey of the reactivity of **1f**, the least electron-deficient tetrazine

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(13) These reagents were found to attack the tetrazine core and initiate azaphilic addition. Faragó, J.; Novák, Z.; Schlosser, G.; Csámpai, A.; Kotschy A. Submitted for publication.

(14) Compound **1a** was heated with 2-methoxy-naphthyl-1-boronic acid in the presence of 5% $Pd(OAc)_2$, 10% PPh_3, and 2 equiv of K_2CO_3 in DMA under argon to give only a highly polar product attributed to the formation of a tetrazine−oxygen bond.

(15) An analogous case was reported recently: Novák, Z.; Szabó, A.; Répási, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327−3329.

in the **1f**−**h** series, toward the constituents of the catalytic system (in DMA at ambient temperature) revealed that CuI or TEA leads to the complete decomposition of **1f** in less than 1 h and Pd(OAc)$_2$ also initiates a similar process. In the presence of (PPh$_3$)$_2$PdCl$_2$, **1f** remained unchanged.

The observation that tetrazines, which undergo Sonogashira coupling, do not react with acetylides in the absence of the catalyst opens up the possibility of the use of zinc acetylides. These compounds can be easily prepared in situ from the appropriate alkyne[17] and were already shown to participate readily in Negishi couplings with electron-deficient heterocycles.[18] The fact that the Negishi coupling runs in the absence of base and copper salt is also encouraging, as its precatalyst, (PPh$_3$)$_2$PdCl$_2$, was tolerated by the otherwise sensitive chlorotetrazine **1f**.

1-Hexynylzinc chloride (**6**), prepared through transmetalation from 1-hexynyllithium and zinc chloride, was reacted with the tetrazines (**1a**−**c**,**f**,**h**) in tetrahydrofuran, in the presence of 7 mol % (PPh$_3$)$_2$PdCl$_2$. Unfortunately, the more reactive chlorotetrazines (**1f**,**h**) gave only decomposition, but the aminotetrazines (**1a**−**c**) furnished the expected products (Figure 1).

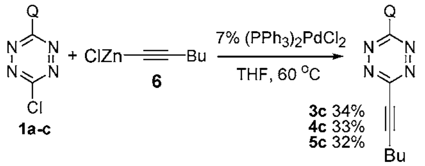

Figure 1. Negishi coupling of chlorotetrazines **1a**−**c** with 1-hexynylzinc chloride (**6**).

The isolated yields were consistently around 30%, and despite the less forcing conditions, decomposition was observed in each case. The presence of a nucleophilic substitution pathway was ruled out in this case too, as heating of **1a**−**c** with **6** in THF in the absence of the catalyst gave no coupled product at all. Attempts were made at extending the coupling to phenylzinc bromide, but again we observed only decomposition of the starting tetrazines.

Although the use of organozinc reagents did not lead to an improvement in terms of the yield of the products, we found these results still encouraging and hope that the range of effective coupling partners might be extended to other organometallic reagents. Research in that direction is currently under way in our laboratory.

It is interesting to note that the analogously substituted chlorotriazines, unlike tetrazines, readily undergo nucleophilic substitution with magnesium acetylides[19] and participate in Negishi[18] and Sonogashira[20] coupling too, underlining the sensitivity of the tetrazine core.

In summary, we demonstrated that, with the careful selection of the reagents and conditions, chlorotetrazines can participate in Sonogashira and Negishi reactions. The described processes allow for the selective introduction of alkynyl substituents onto the tetrazine core and constitute the first example of cross-coupling on this system. Besides their potential as synthons, by virtue of the incorporation of two moieties that are known to react with one another,[21] alkynyltetrazines might also have an interesting role in materials science.

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Supporting Information Available: Experimental procedures and characterization data for the products illustrated in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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