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Convenient synthesis of α-dichloromethylpyridines from 3-trichloromethyl-1,2,4-triazines

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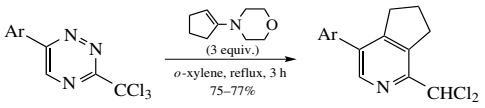
Reaction of 6-aryl-3-trichloromethyl-1,2,4-triazines with 1-morpholinocyclopentene affords 4-aryl-1-dichloromethyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridines.



Pyridine derivatives bearing α-positioned di- or trichloromethyl groups are of considerable interest as they can be easily converted into the corresponding carboxylic acids[1] or aldehydes.[2] Furthermore, α-dichloromethylpyridines are used as plant growth regulators[3] and fungicides.[4] The good solubility in organic solvents is an important factor from the standpoint of analysis of α-dichloromethylpyridines in water or soils.[5] Thus, the development of universal synthetic approaches to such structures is an urgent task.

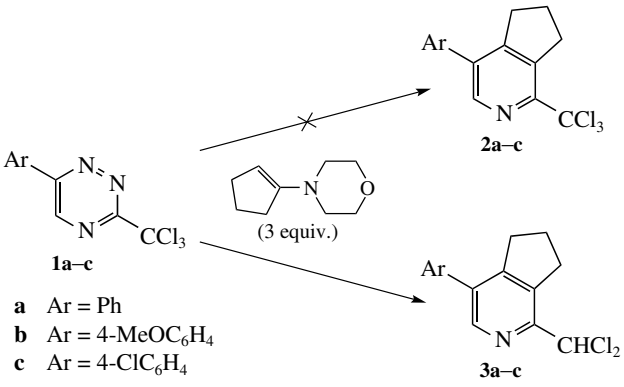
α-Trichloromethylpyridines can be prepared by heterocyclization of trichloroacetonitrile[6] or hexachloroacetone,[7] by exhaustive chlorination of the methyl group, *e.g.*, under the action of thionyl chloride[8] or by substitution of the trifluoromethyl group.[9] α-Dichloromethylpyridines can be synthesized by heterocyclization of less available dichloroacetonitrile[10] or dichloroacetyl chloride,[11] various transformations of the trichloromethyl group,[12] partial chlorination of the methyl group[13] or direct substitution of the difluoromethyl group.[14]

It worth to mention that cases of simultaneous equipping of α-tri- or α-dichloromethylpyridines with additional substituents including cycloalkene fragments are very limited and often require the use of specific reagents, and/or catalysts. For instance, the Ru-catalyzed cycloaddition between 1,6-diynes and corresponding nitriles was used for the synthesis of pyridines,[15] and the reaction of cyclohexylidenepropanedinitrile with trichloroacetonitrile afforded cyclohexene-annelated α-trichloromethylpyridine.[16]

On the other hand, the strategy for the preparation of substituted pyridines *via* their 1,2,4-triazine analogues is well-recognized.[17] It allows one to perform the additional functionalization of positions 3 and 4 of the newly-formed pyridine ring by varying the dienophiles, such as enamines[18] or aryne intermediates.[19] In addition, the introduction of fused cycloalkene moiety is of practical interest due to higher solubility of cycloalkane-annelated pyridines in organic solvents.[20]

However, such a synthesis with objects of the current study was performed only in a single case,[21] although 3- or 5-trichloromethyl-substituted 1,2,4-triazines[22–25] are usually more available compared to α-trichloromethylpyridines.

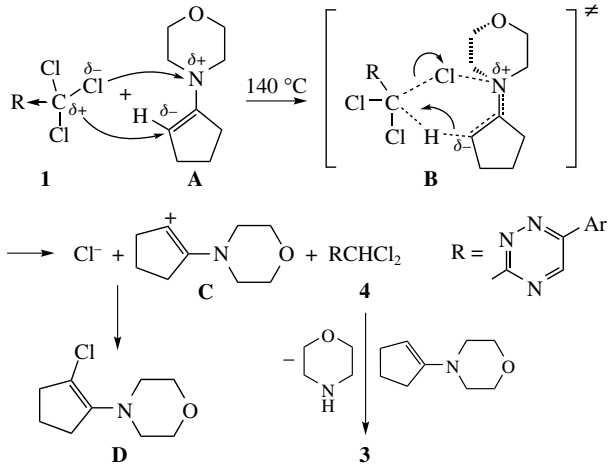
Here, we present an unexpected result of the interaction of known[22] 6-aryl-3-trichloromethyl-1,2,4-triazines **1** with 1-morpholinocyclopentene (3 equiv.) as the dienophile. This reaction did not lead to the expected 1-trichloromethyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridines **2**, while the only products were their synthetically less accessible α-dichloromethyl analogues **3**.[†] Structure of products **3** was proven by mass spectrometry, elemental analysis and NMR spectroscopy. ^{1}H NMR spectra contain the one proton singlet at 6.76–6.83 ppm, corresponding to the α-dichloromethyl group. In the ^{13}C NMR spectra the $CHCl_2$ carbon atom resonated at 70.2–71.4 ppm. In mass spectra (electrospray) the isotopic mass distribution typical of the dichloro-substituted compounds is observed. The expected products **2** were not detected in the reaction mixture even in trace amounts.



Scheme 1 *Conditions*: *o*-xylene, reflux, 3 h.

The literature analysis of the reported examples of the trichloromethyl group conversion into the dichloromethyl one in the aromatic or heteroaromatic[26] compounds (including 1,2,4-tri-

[†] *General method for the synthesis of 4-aryl-1-dichloromehyl-6,7-dihydro-5*H*-cyclopenta[c]pyridines.* The corresponding 3-trichloromethyl-1,2,4-triazine **1** (1 mmol) was suspended in *o*-xylene (40 ml). 1-Morpholinocyclopentene (0.48 ml, 3 mmol) was added and the resulting mixture was stirred under reflux for 3 h. Then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (DCM as eluent). Analytical sample has been obtained by recrystallization (acetonitrile).



Scheme 2

azines[23]) revealed that the use of various reducing agents is one of the key techniques for this purpose. Earlier, the use of enamines as reducing agents, for instance, for the direct conversion of nitro compounds into the corresponding amino derivatives was indicated.[27] Note, that in our case the aza-Diels–Alder reaction affords compounds **3** as the only products depriving alternative pathways of the transformation. Based on these facts, we have proposed a tentative mechanism of product **3** formation.

The charge distribution in the molecule of 1-morpholinocyclopentene **A** is caused by the conjugation between the lone pair of nitrogen atom and the adjacent double bond (Scheme 2). The strong acceptor character of the 1,2,4-triazine should enhance a partial positive charge on the carbon atom of the trichloromethyl group. As a result, this carbon atom gets affinity to the partially negatively charged carbon atom of the enamine. In turn, due to the strong electron-withdrawing effect the chlorine atoms in the trichloromethyl group acquire a partial negative charge, which provides their affinity for the enamine nitrogen atom. As the reaction temperature is high enough (140 °C), the formation of six-atom transition state **B** can take place. After that the proton and electron pair transfer from the enamine to the carbon atom of the former trichloromethyl group occurs to form the dichloromethyl group. Further elimination of both the chloride anion and cation **C** results in chloro-substituted enamine derivative **D**. Thus, the corresponding 3-dichloromethyl-1,2,4-triazine **4** forms only as an intermediate and its subsequent aza-Diels–Alder reaction with enamine excess leads to compound **3**.

It is important that 3-dichloromethyl-1,2,4-triazines are less available than their 3-trichloromethyl analogues.[22,23] Our current findings compensate this drawback making cyclopentene-annelated α-dichloromethylpyridines synthetically more accessible.

In summary, based on the commonly available starting materials and using convenient '1,2,4-triazine' methodology we have provided an efficient method for obtaining fused α-dichloromethylpyridines which can be of interest for further synthetic transformations. A plausible mechanism of this reaction has been described.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.04.014.

*1-Dichloromethyl-4-phenyl-6,7-dihydro-5*H*-cyclopenta[c]pyridine* **3a**. Yield 210 mg (0.75 mmol, 75%), mp 102–104 °C. ^{1}H NMR ($CDCl_3$) δ: 2.17 (m, 2H, 6-CH_2), 3.02 (t, 2H, 7-CH_2, *J* 7.6 Hz), 3.29 (t, 2H, 5-CH_2, *J* 7.6 Hz), 6.86 (s, 1H, $CHCl_2$), 7.37–7.51 (m, 5H, Ph), 8.39 (s, 1H, 3-H). ^{13}C NMR ($CDCl_3$) δ: 25.2, 30.6, 32.4, 71.3 ($CHCl_2$), 128.1, 128.5, 128.7, 135.3, 137.1, 137.7, 146.3, 150.7, 154.1. MS (ESI), *m/z*: 278.05, (calc., *m/z*: 278.05 [M + H]$^+$). Found (%): C, 64.59; H, 4.53; N, 4.80. Calc. for $C_{15}H_{13}Cl_2N$ (%): C, 64.77; H, 4.71; N, 5.04.

For characteristics of compounds **3b,c**, see Online Supplementary Materials.

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