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LETTERS

Solid-phase synthesis of substituted cinnolines by a Richter type cleavage protocol[1]

Stefan Bräse,* Stefan Dahmen and Jean Heuts

RWTH Aachen, Institut für Organische Chemie, Professor-Pirlet-Straße 1, D-52074 Aachen, Germany

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Abstract

Starting from triazene bound *ortho*-halo arenes on a solid support, palladium-catalyzed alkynylations and subsequent cleavage reactions under acidic conditions give rise to *ortho*-alkynylaryldiazonium salts, which in turn undergo cyclization to afford substituted 4-halo- and 4-hydroxycinnolines in moderate to good yields. The method is applicable to automated synthesis. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: solid-phase synthesis; cinnolines; heterocycles; triazenes.

Solid-phase organic synthesis (SPOS) is one of the major tools of combinatorial chemistry.[2–4] The goal for optimal synthetic efficiency lies in the ease of conducting multicomponent and complex transformation reactions.

Recently, we have demonstrated the use of triazenes as linker moieties in SPOS to detach arenes in a traceless manner[5] or conduct cleavage cross-coupling reactions.[6] Furthermore, the use of triazenes as linkers for sensitive amines has been shown.[7]

Until now, the diazonium group, upon cleavage from the resin, has been lost to give dinitrogen. However, in liquid phase a suitable nucleophilic *ortho*-substituent favours cyclization to give heterocyclic structures.[8] This transformation has been known for over a century as a Richter (*ortho*-alkynyl),[9,10] Widman–Stoermer (*ortho*-alkenyl)[11] or Borsche–Koelsch (*ortho*-acetyl)[12] reaction to give cinnoline derivatives, which are interesting building blocks for biologically active compounds. In particular, 4-halocinnolines can serve as valuable starting materials which is due to the ease of substitution by nitrogen nucleophiles. We herein report the first solid-phase Richter reaction.

Starting from benzylaminomethyl polystyrene[13] (1–2% cross-linked with DVB, 100–200 mesh), the required diverse *ortho*-haloaryl resins **1** were prepared from substituted *ortho*-haloanilines in good yields. The palladium-catalyzed cross-coupling under standard conditions [$Pd(OAc)_2$, NEt_3, DMF, 80°C] with different alkynes (trimethylsilylethyne, phenylethyne, 1-heptyne, 1-benzyloxy-1-ethynylcyclopentane) afforded *ortho*-alkynylarene resins **2**. It should be noted that copper was omitted due to the coordination

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* Corresponding author. Fax: +(49) (0) 241/8888127; e-mail: braese@oc.rwth-aachen.de

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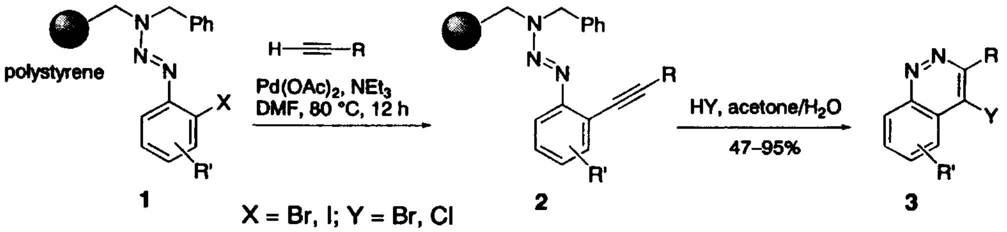
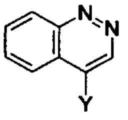
to the triazene moiety, hence leading to traces of copper in the final product. In addition, copper derivatives are more toxic than the palladium analogues. The Richter cleavage reactions were conducted with aqueous hydrogen chloride or hydrogen bromide in acetone at room temperature (1 h). Filtration and dilution with water afforded the cinnolines **4**–**8** in 47–95% yield and with 60–95% purity without any further purification (NMR, GC, GC–MS).[14] The cleavage was also successfully conducted in a 2×11 matrix on the Bohdan MiniBlock.

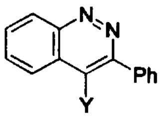
While under more acidic conditions (20 equiv. of acid, 1 molar), trimethylsilylethyne can serve as an ethyne equivalent due to loss of the silyl group, dilute acid favours the formation of silyl derivatives like **6**-Br. Hydrogen fluoride or hydrogen iodide failed to give the desired compounds. Longer reaction times led to increased formation of 4-hydroxycinnolines by a hydrolysis reaction (e.g. **5**-OH, **4**-OH, 40–65% yield), which also have been found as major products when conducting the reaction in a more diluted acidic solution (2 equiv. of acid, 0.1 molar).[15]

In conclusion, the solid-phase synthesis of diverse substituted cinnoline derivatives is presented. Similar work on the construction of other heterocyclic systems[8–12] is in progress.

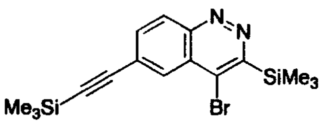




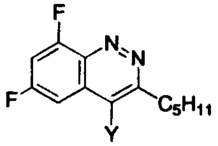
4-OH,Cl



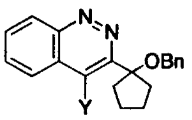
5-OH,Cl,Br



6-Br



7-Br,Cl



8-Br,Cl

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