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Alkynylation-Desilylation-Alkynylation-Cycloisomerization (ADAC) Three-Component Synthesis of 2,2’-Biindolyls – Concise Synthesis of Tjipanazole I

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Dedicated to Prof. Dr. Claus A. M. Seidel on the occasion of his 60th birthday.

A sequentially Pd/Cu-catalyzed alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) process in the sense of a consecutive three-component reaction using TIPS-butadiyne as a four carbon building block gives a rapid and efficient access to 2,2’-biindolyls in a one-pot fashion. This facile entry to unsymmetrically substituted title compounds has been employed in a concise two-step synthesis of the alga alkaloid tjipanazole I.

Multicomponent Reactions (MCR)[1] are characterized by the formation of more than two bonds from more than two compounds in a one-pot reaction. Consequently, this multifaceted reactivity based concept[2] has opened many avenues from reaction design[3] over natural product syntheses[4] and diversity-oriented syntheses[5] to sustainable organic syntheses[6] and application in medicinal chemistry.[7] MCR syntheses of heterocycles[8] are particularly attractive, because they provide many scaffolds for the development of lead structures in active pharmaceutical ingredients[9] and functional molecules for advanced photonic and electronic technologies.[10] MCR syntheses of heterocycles catalyzed or initiated by transition metal catalysis even more enhance the versatility of this highly efficient and efficacious concept.[11]

The 2,2’-biindolyl ligation (Figure 1) is present in indigoids, indolocarbazole and indolotryptoline alkaloids.[12]

Most prominently, staurosporine, an indolo[2,3-α]carbazole alkaloid, and related compounds reveal potent protein kinase inhibition,[13] which is particularly interesting for developing anticancer therapeutics.[14] Tjipanazole I, isolated from blue-green alga Tolypothrix tjipanasensis, turned out to show antifungal activity.[15] Interestingly, tjipanazole I is accessible in a straightforward cyclocondensation with 2,2-dioxy-N,N-dimethylamine starting from an unsymmetrically substituted 2,2’-biindolyl.[16] Finally, unsymmetrically halogen substituted 2,2’-biindolyls have been shown to efficiently inhibit MRSA-pyruvate kinase with high antibacterial activity against Staphylococcus aureus ATCC 29213, however, without significant cytotoxicity in mammals.[17]

While symmetrically substituted 2,2’-biindolyls are accessible by Madelung cyclization of N-aryloxamides,[18] cycloisomerization of 1,4-bis(ortho-aminoaryl)-1,3-butadiynes,[19] Ir-catalyzed cyclization of 2-ethynyl anilines,[20] or protecting group directed metal catalyzed homocoupling of indoles,[21] concise syntheses of unsymmetrically substituted 2,2’-biindolyl derivatives still remain a major challenge. Although 2-iodo indoles can be coupled to the title compounds by Pd-catalyzed coupling with stannanes (Stille coupling)[22] or boronic acids (Suzuki coupling),[23] often the starting materials have to be prepared in multistep reactions. In 2003 for the total synthesis of tjipanaizes B, D, E, and I, Davies and coworkers reported a robust multistep approach to 2,2’-biindolyls using an ortho-nitrotoluene aldol-type condensation followed by Cadogan-Sundberg cyclization or Pd-catalyzed reductive cyclization. [16]

In recent years, starting with catalytic generation of alkynoyl intermediates as an entry to consecutive multicomponent syntheses of many classes of functional heterocycles[24] we

Figure 1. 2,2’-Biindolyl, indolo[2,3-α]carbazole alkaloids staurosporine and tjipanazole I, and antibacterial MRSA-pyruvate kinase inhibitors.
became increasingly interested in sequentially Pd-catalyzed processes,\textsuperscript{[25]} in particular for developing them for one-pot syntheses of heterocycles.\textsuperscript{[25e]} Inspired by our one-pot coupling-cyclization synthesis of (aza)indoles\textsuperscript{[26]} and the implementation of TIPS-butadiyne as an ideal C4-building block in sequentially catalyzed MCR-formations of triazole derivatives\textsuperscript{[27]} we reasoned that unsymmetrically substituted 2,2'-biindolyls might be accessible in a one-pot fashion by sequential Sonogashira alkynylation with TIPS-butadiyne followed by base-catalyzed cycloisomerization in the sense of a MCR. Here, we communicate our first findings on a consecutive three-component alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) synthesis of unsymmetrically substituted 2,2'-biindolyls.

De novo ring formation starting from ortho-iodo anilines 1 (and 1') as versatile and readily available substrates is particularly attractive for devising a retrosynthetic analysis of 2,2'-biindolyls 3 (Scheme 1).

The unsymmetrical nature of TIPS-protected butadiyne (2) allows the formation of unsymmetrically substituted diynes 4 and 5 by intermediate desilylation in a one-pot fashion. Based upon the catalytic generation of pentadiynones and pyrazolyl-triazoles thereof\textsuperscript{[27b]} and 1H-1,2,3-triazol-4-yl-pyrrolo[2,3-b]pyridines,\textsuperscript{[27a]} both in a consecutive one-pot fashion, the ADAC one-pot sequence was conceptualized to begin with an alkynylation of an ortho-iodo aniline 1 with TIPS-butadiyne (2) furnishing the coupled butadiyne 4. Thereof, desilylation and alkynylation uniquely generate the unsymmetrically substituted butadiyne 5, which in turn cycloisomerizes by two-fold base-mediated 5-endo-dig cyclization to furnish the title compounds.

Scheme 1. Retrosynthetic analysis of unsymmetrically substituted 2,2’-biindolyls by one-pot alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) sequence (TIPS = triisopropylsilyl).

Scheme 2. Consecutive three-component alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) synthesis of unsymmetrically substituted 2,2’-biindolyls.
The individual steps and their concatenation to a one-pot sequence were optimized to identify the most optimal reaction conditions (see Supporting Information).

With optimized conditions for the one-pot synthesis of 2,2′-biindolyl 3a in hand we set out to check the scope of this novel consecutive three-component synthesis by varying the substitution pattern on the 2-iodo aniline derivatives 1. The versatility of this process was illustrated by the synthesis of 17 examples in yields from 35 to 88% (Scheme 2).[20]

Taking into account that four new bonds and two rings are being formed in this one-pot process the average bond forming yield amounts to 77–97%. Interestingly, the electronic nature of substituents on the aniline aryl ring of substrate 1 and 1′ can be electron-rich, electron-poor and even chloro and bromo substituents can be carried through the sequence uneventfully. N-Methyl and benzyl substituted anilines 1’ are also tolerated (see products 3p and 3q), which are perfectly suited for desymmetrizing applications in complex molecules synthesis. In this study, we primarily employed commercially available substituted anilines 1 and 1’, yet, 2-iodo-5-methylaniline (1e) and 2-benzylxy-6-iodoaniline (1j) were successfully employed to demonstrate the accessibility of substitution patterns at 7- and 6-positions in title molecules 3 (see products 3d and 3i).

Most favorably, the three components are efficiently reacted in an almost equistoichiometric ratio to give the desired target compounds in good yield. It is noteworthy mentioning that an N-tosyl substituent is not tolerated, because it is cleaved under catalyzed sequence. The scope of the substitution pattern of this novel ADAC synthesis has successfully applied to a two-step synthesis of tijpanazole I in higher yield than the published three-step synthesis. Studies directed to expand the diversity oriented scope to complex functionalization of 2,2′-biindolys, their use in alkaloid syntheses and evaluation of MRSA inhibition are currently underway.

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Conflict of Interest

The authors declare no conflict of interest.

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