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HETEROCYCLES IN FOCUS

The synthesis of *ortho*-stilbazoles (2-styrylpyridines) (microreview)

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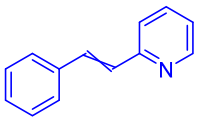


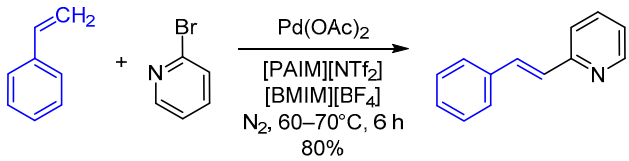
This microreview compiles methods for the synthesis of *ortho*-stilbazoles (2-styrylpyridines) described in the literature in 2017–2022. Depending on the synthons from which the target structure is formed, four main synthetic approaches can be distinguished: coupling reactions, Wittig reactions, condensation reactions, and pyridine ring formation reactions.

Introduction

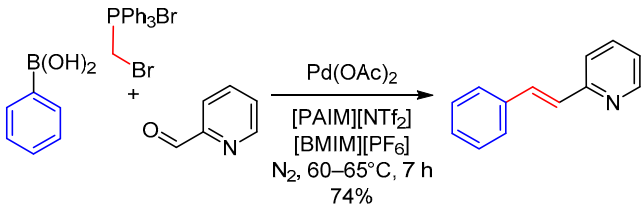
Organic molecules based on the framework of *ortho*-stilbazole are widely employed in medicinal chemistry[1] and materials chemistry.[2] Such heterocycles exhibit high antioxidant,[1a,b] antitumor,[1c] and anti-inflammatory activity.[1d] The possibility of inhibiting the replication of the SARS-CoV-2 coronavirus,[1e] VEGFR-2 kinase,[1f] and Mur ligase[1g] has also been noted. Conjugated molecules based on *ortho*-stilbazole are used as chemosensors for the determination of $Cr_2O_7^{2-}$ and MnO_4^-,[2a] CN^-,[2b] F^-, and AcO^-[2c] anions, Hg^{2+},[2d] Zn^{2+},[2e] 2,4,6-trinitrophenol[2f] cations, as fluorescent probes and labels,[2g] as candidate materials for photonic devices and optical switches.[2h]

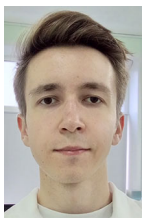
Coupling reactions

The coupling reactions are one of the principal methods for the synthesis of *ortho*-stilbazoles.[1g,3] The Heck reaction based on the use of styrene and 2-bromopyridine can be provided as a classical example. A feature of the transformation is the use of ionic liquids.[3a]



The $[PAIM][NTf_2]/[BMIM][X]$ (X = PF_6, BF_4) system also demonstrated its efficacy in promoting the original tandem Wittig–Suzuki reaction.[3a] Both transformations involving ionic liquids proceed stereoselectively with the formation of the *E*-isomers.





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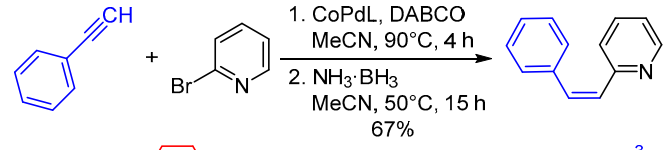
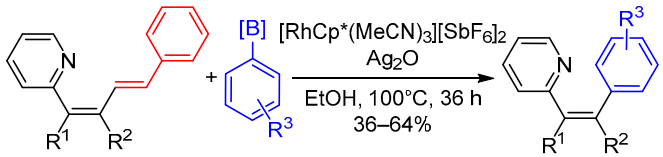
Coupling reactions (continued)

The elusive *Z*-isomer of *ortho*-stilbazole can be obtained by a one-pot synthesis.[3b] For this, the sequence of the Sonogashira coupling in the presence of a cobalt-palladium catalyst and the semihydrogenation of alkynes with borazane is employed.

The original rhodium(III)-catalyzed Suzuki reaction of 1,3-dienes with arylboronic acids is accompanied by elimination of the styrene fragment and proceeds with excellent chemoselectivity.[3c] The conversion is carried out in the presence of silver oxide to regenerate the catalyst and return it to the catalytic cycle.

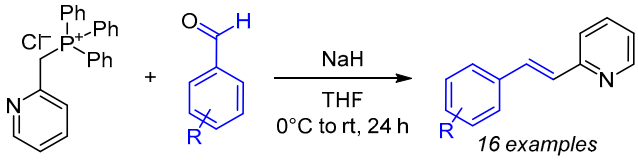




[B] = $B(OH)_2$, Bpin
R^1 = Me, Ar; R^2 = Me, Ar; $R^1 + R^2$ = cycloalkyl
R^3 = Alk, Ar, Hal, OMe, CO_2Me, $CH_2CH(NHBoc)CO_2Me$

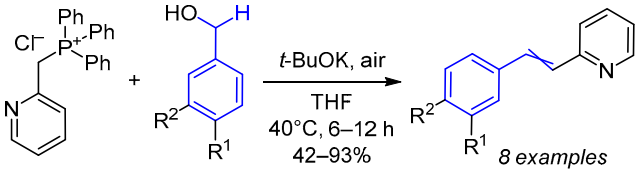
The Wittig reaction

The classical Wittig reaction remains one of the most accessible and versatile tool in the synthesis of styrylpyridines.[1c,2f,4] One example of the application of the Wittig reaction in the synthesis of styrylpyridines is the reaction of benzaldehyde derivatives with 2-picolylphosphonium chloride in the presence of NaH.[4a]



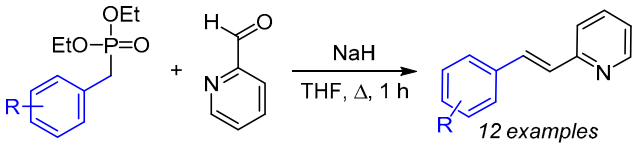
R = H, Alk, Ar, Ac, Hal, SMe, OMe, OCF_3, OAc, CO_2Me, NO_2

A method of direct Wittig olefination of alcohols was proposed. The reaction was carried out under aerobic conditions using air as an inexpensive and clean oxidizing agent. *ortho*-Stilbazoles were formed as a mixture of stereoisomers with a significant predominance of the *E*-isomer.[4b]



R^1 = H, Me, Ph, COPh, Cl, NO_2, Br; R^2 = H; $R^1 + R^2$ = OCH_2O

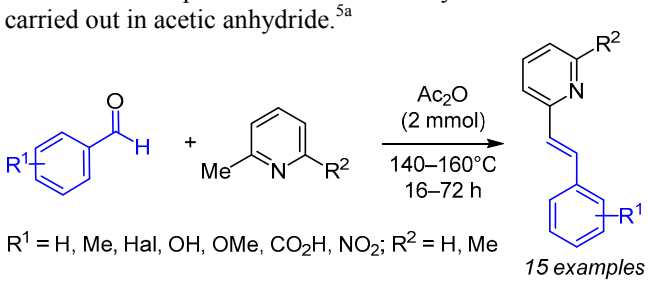
A modified Wittig reaction, the Horner–Wadsworth–Emmons reaction, is also used for the synthesis of derivatives of *ortho*-stilbazole. In this case, the transformations proceed with the participation of pyridine-2-carbaldehyde and benzylphosphonate in the presence of a base.[4c]



R = H, Me, OMe, Hal, CF_3, CN

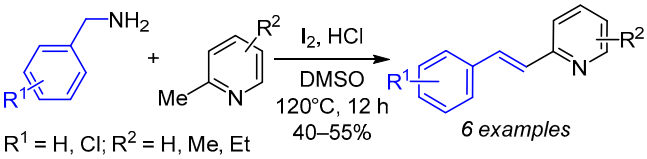
Condensation reactions

Condensation reactions are one of the simplest approaches to the synthesis of *ortho*-stilbazoles.[1a,b,5] For example, reactions between α-picolines and benzaldehyde derivatives are carried out in acetic anhydride.[5a]



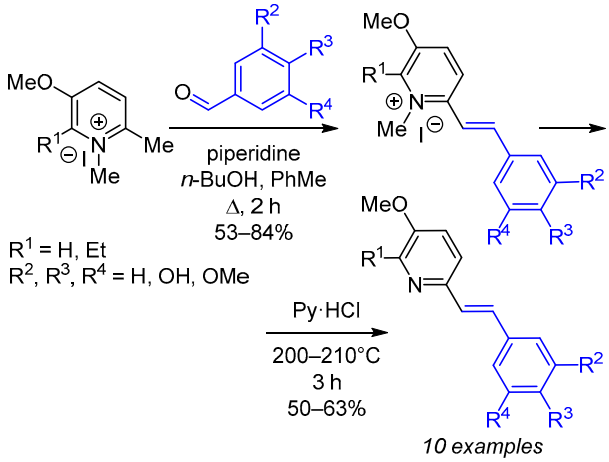
R^1 = H, Me, Hal, OH, OMe, CO_2H, NO_2; R^2 = H, Me

An innovative synthesis of 2-styrylpyridines from benzylamines and *ortho*-picolines in DMSO medium with the addition of HCl and iodine as an oxidizing agent was shown.[5b]



R^1 = H, Cl; R^2 = H, Me, Et

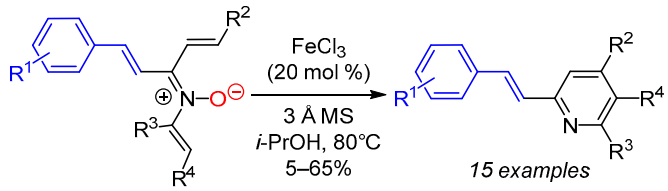
These transformations were also carried out using methylpyridinium salts in *n*-butanol[1b] or a *n*-butanol–toluene mixture.[1a] Demethylation of salts of the compounds was carried out by heating to 210°C with anhydrous pyridinium chloride. In this case, the time of the condensation step was significantly reduced.



R^1 = H, Et
R^2, R^3, R^4 = H, OH, OMe

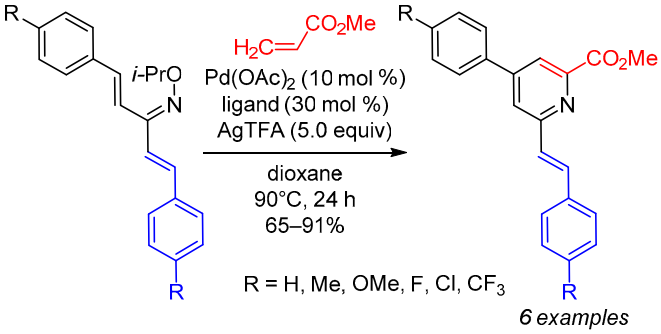
Pyridine ring formation reactions

Heterocyclization[6] or trans-heterocyclization[7] reactions are also widely employed for the preparation of *ortho*-stilbazole derivatives. A method of synthesis from *N*-vinyl-α,β-unsaturated nitrones in the presence of an iron catalyst and molecular sieves *via* cleavage of the N^+–O^- bond was presented.[6a]

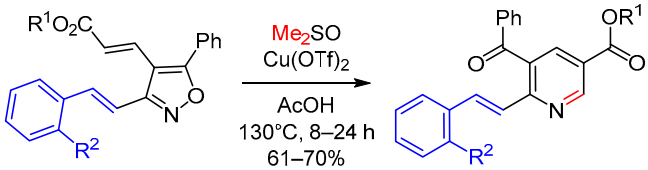


R^1 = H, Me, OMe, Br, CF_3; R^2, R^3, R^4 = H, Alk, Cy, Ar

It was shown that oximes, close structural analogs of nitrones, can be used instead by reacting them with methyl acrylates.[6b] In this case, palladium(II) acetate with the ligand (2,6-bis-(adamantan-1-yl)oxypyridine) and a silver salt were used as the catalyst and as an oxidizing agent, respectively.

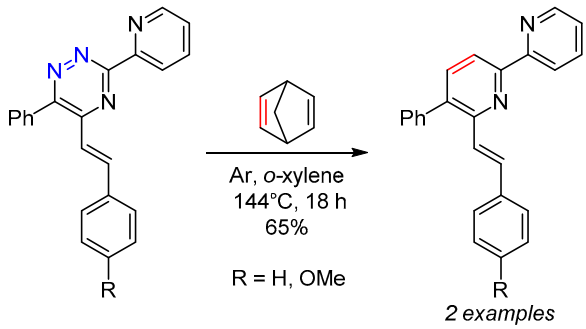


An example of a trans-heterocyclization reaction is the conversion of isoxazoles.[7a] The copper catalyst initiates ring opening by cleaving the N–O bond. DMSO serves as a one-carbon synthon generating an active methylene group in the course of the reaction, which leads to the formation of two C–C bonds during the formation of the pyridine ring.



R^1 = Me, Et; R^2 = H, NO_2

The reaction of 1,2,4-triazine derivatives with norbornadiene proceeds according to the mechanism of the aza-Diels–Alder reaction.[7b] The transformations result in the elimination of a nitrogen molecule and formation of the pyridine ring at the expense of two carbon atoms of the diene.



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