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

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Introduction

Organic molecules based on the framework of ortho-stilbazole are widely employed in medicinal chemistry1 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 ligase1g has also been noted. Conjugated molecules based on ortho-stilbazole are used as chemosensors for the determination of Cr2O72− and MnO4−,2a CN−,2b F−, and AcO−2c anions, Hg2+,2d Zn2+,2e 2,4,6-trinitrophenol2f 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][NTf2]/[BMIM][X] (X = PF6, BF4) 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. For this, the sequence of the Sonogashira coupling in the presence of a cobalt-palladium catalyst and the semihydrogenation of alkenes 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. The conversion is carried out in the presence of silver oxide to regenerate the catalyst and return it to the catalytic cycle.

The Wittig reaction

The classical Wittig reaction remains one of the most accessible and versatile tool in the synthesis of styrylpyridines. One example of the application of the Wittig reaction in the synthesis of styrylpyridines is the reaction of benzaldehyde derivatives with 2-picolylyphosphonium chloride in the presence of NaH.

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.

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.

Condensation reactions

Condensation reactions are one of the simplest approaches to the synthesis of ortho-stilbazoles. For example, reactions between α-picoline and benzaldehyde derivatives are carried out in acetic anhydride.

An innovative synthesis of 2-styrylpyridines from benzylamines and ortho-picoline in DMSO medium with the addition of HCl and iodine as an oxidizing agent was shown.
Pyridine ring formation reactions

Heterocyclization or trans-heterocyclization 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.

It was shown that oximes, close structural analogs of nitrones, can be used instead by reacting them with methyl acrylates. It was shown that oximes, close structural analogs of nitrones, can be used instead by reacting them with methyl acrylates. In this case, palladium(II) acetate with the ligand (2,6-bis-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.

An example of a trans-heterocyclization reaction is the conversion of isoxazoles. 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.

The reaction of 1,2,4-triazine derivatives with norbornadiene proceeds according to the mechanism of the aza-Diels–Alder reaction. 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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References

1. (a) Semenov, A. V.; Balakireva, O. I.; Tarasova, I. V.; Semenova, E. V.; Zulfugarov, P. K. Med. Chem. Res. 2020, 29, 1590. (b) Semenov, A. V.; Balakireva, O. I.; Tarasova, I. V.; Burtasov, A. A.; Semenova, E. V.; Petrov, P. S.; Minaeva, O. V.; Pyataev, N. A. Med. Chem. Res. 2018, 27, 1298.

2. (c) Pugachev, M. V.; Pavelev, R. S.; Nguyen, T. N. T.; Gabbasova, R. R.; Bulatov, T. M.; Iskannova, A. G.; Aljondi, B.; Bondar, O. V.; Grishaev, D. Yu.; Yamaleeva, Z. R.; Kataeva, O. N.; Nikishova, T. V.; Balakin, K. V.; Shtyrlin, Y. G. Bioorg. Med. Chem. 2021, 30, 115957. (d) Chen, G.; Shan, W.; Wu, Y.; Ren, L.; Dong, J.; Ji, Z. Chem. Pharm. Bull. 2005, 53, 1587. (e) Li, Y.-Q.; Li, Z.-L.; Zhao, W.-J.; Wen, R.-X.; Meng, Q.-W.; Zeng, Y. Eur. J. Med. Chem. 2006, 41, 1084. (f) Sun, W.; Fang, S.; Yan, H. Med. Chem. Commun. 2018, 9, 1054. (g) Harst, M.; Frlan, R.; Knez, D.; Zdovic, I.; Barretteau, H.; Gobec, S. Bioorg. Med. Chem. Lett. 2021, 40, 127866.

3. (a) Semenov, A. V.; Balakireva, O. I.; Tarasova, I. V.; Semenova, E. V.; Zulfugarov, P. K. Med. Chem. Res. 2020, 29, 1590. (b) Semenov, A. V.; Balakireva, O. I.; Tarasova, I. V.; Burtasov, A. A.; Semenova, E. V.; Petrov, P. S.; Minaeva, O. V.; Pyataev, N. A. Med. Chem. Res. 2018, 27, 1298.

4. (c) Pugachev, M. V.; Pavelev, R. S.; Nguyen, T. N. T.; Gabbasova, R. R.; Bulatov, T. M.; Iskannova, A. G.; Aljondi, B.; Bondar, O. V.; Grishaev, D. Yu.; Yamaleeva, Z. R.; Kataeva, O. N.; Nikishova, T. V.; Balakin, K. V.; Shtyrlin, Y. G. Bioorg. Med. Chem. 2021, 30, 115957. (d) Chen, G.; Shan, W.; Wu, Y.; Ren, L.; Dong, J.; Ji, Z. Chem. Pharm. Bull. 2005, 53, 1587. (e) Li, Y.-Q.; Li, Z.-L.; Zhao, W.-J.; Wen, R.-X.; Meng, Q.-W.; Zeng, Y. Eur. J. Med. Chem. 2006, 41, 1084. (f) Sun, W.; Fang, S.; Yan, H. Med. Chem. Commun. 2018, 9, 1054. (g) Harst, M.; Frlan, R.; Knez, D.; Zdovic, I.; Barretteau, H.; Gobec, S. Bioorg. Med. Chem. Lett. 2021, 40, 127866.

5. (a) Semenov, A. V.; Balakireva, O. I.; Tarasova, I. V.; Semenova, E. V.; Zulfugarov, P. K. Med. Chem. Res. 2020, 29, 1590. (b) Semenov, A. V.; Balakireva, O. I.; Tarasova, I. V.; Burtasov, A. A.; Semenova, E. V.; Petrov, P. S.; Minaeva, O. V.; Pyataev, N. A. Med. Chem. Res. 2018, 27, 1298.

6. (a) Zhang, X.-D.; Zhao, Y.; Chen, K.; Jiang, Y.-F.; Sun, W.-Y. Chem.–Asian J. 2019, 14, 3620. (b) Guan, R.; Chen, H.; Cao, F.; Cao, D.; Deng, Y. Inorg. Chem. Commun. 2013, 38, 112. (c) Xie, P.; Guo F.; Zhang, D.; Zhang, L. Chin. J. Chem. 2011, 29, 1975. (d) Zhao, H.; Sun, L.; Chen, W.; Tian, G.; Chen, Y.; Li, Y.; Su, J. Tetrahedron 2016, 72, 2300. (e) Gabr, M. T.; Pigge, F. C. Dalton Trans. 2016, 45, 14039. (f) Zhang, X.-D.; Hua, J.-A.; Guo, J.-H.; Zhao, Y.; Sun, W.-Y. J. Mater. Chem. C 2018, 6, 12623. (g) Wang, M.-Q.; Ren, G.-Y.; Zhao, S.; Lian, G.-C.; Chen, T.-C.; Ci, Y.; Li, H.-Y. Spectrochim. Acta A: Mol. Biomol. Spectrosc. 2018, 199, 441. (h) Senthilk., K.; Kalainathan, S.; Kumar, A. R.; Aravindan, P. G. RSC Adv. 2014, 4, 56112.