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Chemistry of Heterocyclic Compounds **2017**, *53*(2), 153–155

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indoles (microreview)

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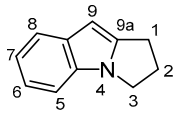


This microreview, devoted to the methods that are applicable to the synthesis of 2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]indole derivatives, is illustrated by recently published examples, which have been organized according to the type of bond created.

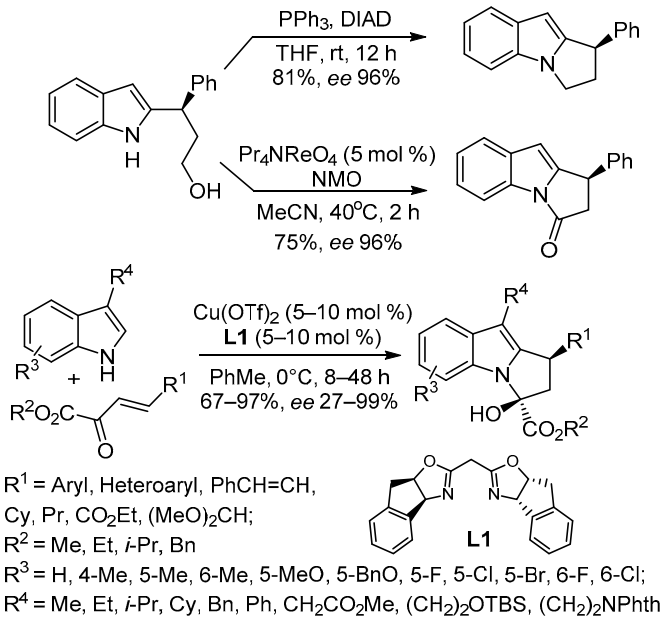
Introduction

The tricyclic 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core is a structural motif in a range of natural indole alkaloids, such as the bisindole alkaloids flinderoles, isolated from plants belonging to the genus *Flindersia* within the project aimed at searching for new antimalarials.[1] Derivatives of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole have shown a potential for the treatment of autoimmune conditions[2,3] ($S1P_1$ receptor agonists), obesity[4] ($5\text{-}HT_{2c}$ receptor agonists), diabetes[5] (selective inhibitors of PKCβ-protein kinase). Besides that, such compounds exhibit anti-inflammatory, analgetic,[6] and anticancer properties,[7,8] providing motivation for the elaboration of advanced catalytic methodologies for their synthesis.

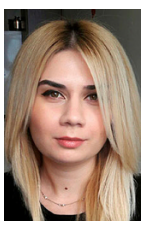
Formation of the C(3)–N bond

According to this synthetic strategy, the most frequently used approach is intramolecular alkylation of indole nitrogen atom with halides or mesylates.[9] Furthermore, the corresponding alcohol was used directly under the Mitsunobu reaction conditions to obtain chiral tricyclic derivatives. Cyclization of the same compound under oxidative conditions gave a tricyclic amide.[10]

The assembly of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole ring was performed by a cascade reaction of indoles with dielectrophilic α-keto-β,γ-unsaturated esters. The Michael reaction product that formed at the first stage of this process underwent a spontaneous hemiacetalization, leading to a tricyclic product in a high yield. An employment of an optimal chiral bis(oxazoline) ligand allowed for achieving high, often complete enantioselectivity. The only limitation of this reaction was the presence of an alkyl substituent in the starting enone (R^1 = Pr, R^2 = Et, 67% yield, *ee* 27%).[11]



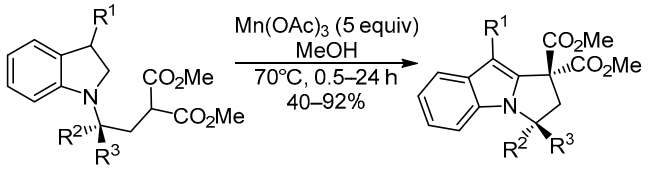
R^1 = Aryl, Heteroaryl, PhCH=CH, Cy, Pr, CO_2Et, $(MeO)_2CH$;
R^2 = Me, Et, *i*-Pr, Bn
R^3 = H, 4-Me, 5-Me, 6-Me, 5-MeO, 5-BnO, 5-F, 5-Cl, 5-Br, 6-F, 6-Cl;
R^4 = Me, Et, *i*-Pr, Cy, Bn, Ph, CH_2CO_2Me, $(CH_2)_2OTBS$, $(CH_2)_2NPhth$



Anastasiya Tairovna Plieva was born in 1988 in Tskhinvali, Georgian SSR. She graduated from the Chemical Technology Faculty of North-Ossetian State University (NOSU) in 2010 and continued graduate studies at NOSU in 2011–2014 under the guidance of Professor, Doctor of Chemical Sciences V. T. Abaev. Currently employed as Assistant at the Chair of Organic Chemistry of NOSU. The area of scientific interests includes the chemistry of heterocyclic compounds, chemistry of azides, and electrochemistry of organic compounds.

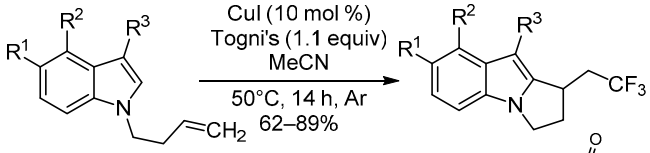
Formation of the C(1)–C(9a) bond

Intramolecular alkylation of indole ring by electron-poor malonyl radicals is a key step in a two-stage synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole derivatives.[12] According to this scheme, indolines were alkylated with donor-acceptor cyclopropanes in the presence of 10% $Sc(OTf)_3$ or 5% $Yb(OTf)_3$, and the obtained *N*-substituted indolines were treated with an excess of $Mn(OAc)_3$, combining the aromatization and simultaneous annulation of the indole ring.



R^1 = H, $(CH_2)_2$OTBS, CH_2CN, $(CH_2)_2$NPhth
R^2 = Ph, HC≡C, EtC≡C, PhC≡C, H_2C=CH, 4-BrC_6H_4, 4-ClC_6H_4, *i*-Pr, 2-furyl, 2-naphthyl; R^3= H, Me

The cyclization of *N*-homoallylindoles in the presence of Togni's reagent produced trifluoroethyl derivatives of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole.[13] The reaction mechanism, as proposed by the authors, involved the generation of trifluoromethyl radical from the reduction of Togni's reagent with copper(I) and its subsequent addition to the alkene double bond. Further oxidation of the intermediate alkyl radical to the respective cation resulted in cyclization at position 2 of the indole ring.

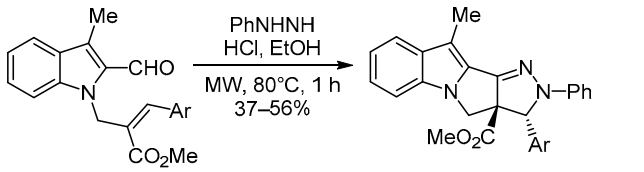


R^1 = H, Br; R^2 = H, Me;
R^3 = Me, Et, *t*-Bu, *c*-Pr, Cl, Br, SH, OMe, CH_2OH, CH_2CN, CHO, CO_2H, CN

Togni's reagent

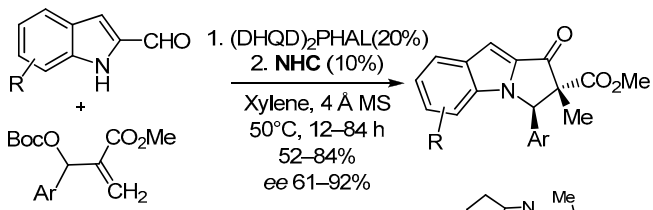
Formation of the C(1)–C(2) bond

The (3+2) cycloaddition of azomethine imines to a double bond has been used in the synthesis of pyrazolopyrroloindoles.[14] However, complex mixtures were formed in the case of 2- and 4-nitrophenyl derivatives, and the target products were not isolated. It is interesting to note that the authors managed to perform the entire three-stage reaction sequence as a one-pot procedure, combining the *N*-alkylation and formylation of 3-methylindole with the subsequent condensation involving aryl hydrazines. The efficiency of such process showcased with five examples (20–27%) appeared to be comparable to the stepwise reaction sequence.



Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-EtC_6H_4, 4-(*i*-Pr)C_6H_4, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 4-$MeOC_6H_4$, thiophen-2-yl, 1-naphthyl, 3,4-$(OCH_2O)C_6H_3$

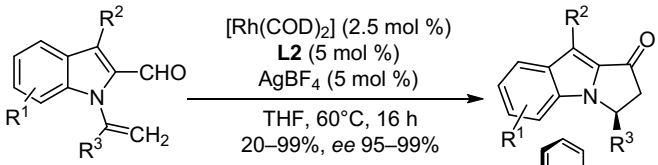
The unusual hydroacylation reaction, leading to the formation of anti-Stetter regioisomer, proceeded in the presence of nucleophilic carbenes.[15] An asymmetric variant of the annulation was designed by using the commercially available cinchona alkaloid derivative 1,4-phthalazindiyl- hydroquinidine ($(DHQD)_2PHAL$). The alkylation of 2-formylindole in the presence of $(DHQD)_2PHAL$ with racemic Morita–Baylis–Hillman carbonate produced an optically active intermediate. The addition of the nucleophilic carbene precursor at the second stage induced hydroacylation with an enantioselective formation of asymmetric quaternary carbon atom.



R = H, 5-Cl, 5-MeO, 4-MeO;
Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4,4-BrC_6H_4, 4-$F_3CC_6H_4$, 4-NCC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-FC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 2-MeC_6H_4, 1-naphthyl, 2-naphthyl, cynnamyl, thiophen-2-yl, Cy

NHC

Enantioselective hydroacylation in the case of *N*-vinylindoles was enabled by using a rhodium catalyst in the presence of a chiral diphosphine ligand.[16] Cyclohexyl derivative, as well as electron-withdrawing 4-trifluoromethyl derivative, in this reaction gave a minimal yield of the product. In the latter case the yield could be improved from 30 to 70% by doubling the load of rhodium catalyst.

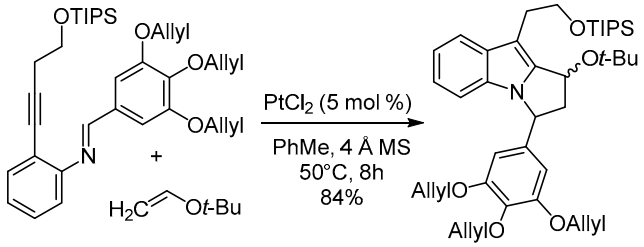


R^1 = H, 4-MeO, 5-MeO, 4-F, 5-Cl 5-CF_3;
R^2 = H, Et; R^3 = Me, Cy, Ph, 3,4,5-$(MeO)_3C_6H_2$ 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-ClC_6H_4, 4-$F_3CC_6H_4$

L2

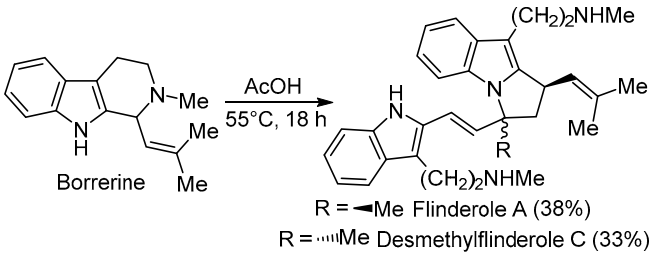
Simultaneous formation of the pyrrolizidine ring

A (3+2) cycloaddition reaction of azomethine ylide, generated by the action of $PtCl_2$, with *tert*-butyl vinyl ether was employed as a key step in the total synthesis of the four possible stereoisomers of juremamine. As a result, the structure assigned to this psychoactive phytoindole, isolated from the bark of *Mimosa tenuiflora* plant, was revised.[17]

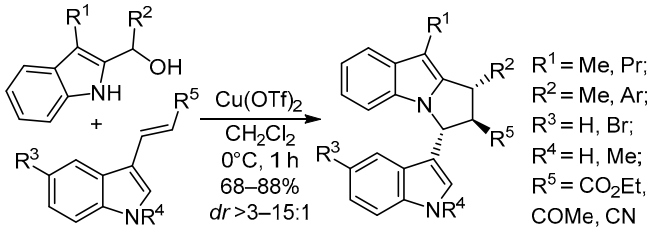


(6+2) Cycloaddition

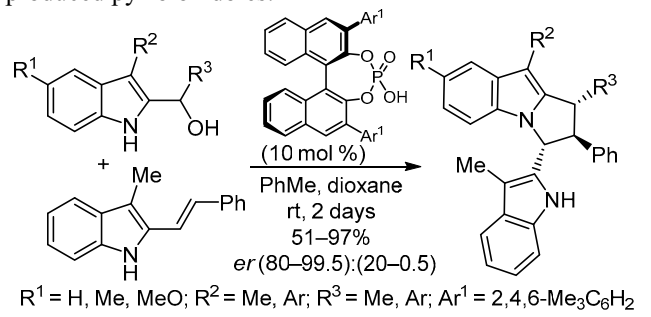
These reactions proceed with the participation of indolidenium cations, generated from the corresponding alcohol or alkene. Thus, the antimalarial alkaloids flinderole and isoborreverine were obtained from tryptamine in a three-step reaction,[18] which was more effective than the previously described 14-step[19] and 19-step[20] syntheses of flinderoles. The key stage of this synthesis was an acid-catalyzed dimerization of borrerine.



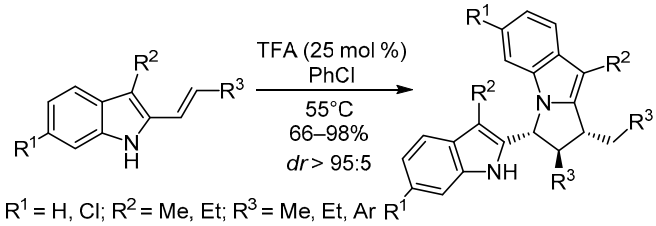
The cycloaddition of indole-2-carbinols to indole-3-acrylic acid gave rise to derivatives of pyrroloindole in high yields and diastereomeric excess.[21]



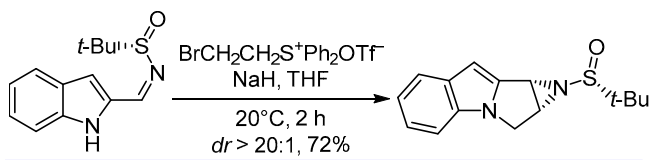
The related reaction involving 3-styrylindoles in the presence of chiral binaphthyl phosphoric acids also produced pyrroloindoles.[22]



Homodimerization of 2-styrylindoles followed the same course in the presence of trifluoromethanesulfonic acid.[23]



The annulation of pyrrole ring with vinylsulfonium salts proceeded with simultaneous formation of aziridine ring.[24]



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