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PALLADIUM-FREE ETHYNYLATION OF PYRROLES AND INDOLES WITH HALOALKYNES IN METAL OXIDES AND SALTS MEDIUM

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New palladium-free cross-coupling between substituted pyrroles, 4,5,6,7-tetrahydroindoles or indoles and haloacetylenes in metal oxides and salts medium (MgO, CaO, ZnO, BaO, Al_2O_3, K_2CO_3) regioselectively affording 2-ethynylpyrroles, 2-ethynyl-4,5,6,7-tetrahydroindoles or 3-ethynylindoles is discussed. The reactions proceed at room temperature under solvent-free conditions without catalysts. The yields of ethynylation products most often range from 60 to 70 %, in certain cases reaching 90–94 %. Refs 35. Tables 1.

Keywords: cross-coupling, haloacylacetylenes, halopropynoates, indoles, pyrroles, metal oxides and salts, 2-acylethynylpyrroles, ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates.

Л. Н. Собенина, Б. А. Трофимов

БЕСПАЛЛАДИЕВОЕ ЭТИНИЛИРОВАНИЕ ПИРРОЛОВ И ИНДОЛОВ ГАЛОГЕНАЛКИНАМИ В ПРИСУТСТВИИ СОЛЕЙ И ОКСИДОВ МЕТАЛЛОВ

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Обсуждается новое беспалладиевое кросс-сочетание замещённых пирролов, 4,5,6,7-тетрагидроиндолов или индолов с галогеноацетиленами в присутствии оксидов металлов и их солей (MgO, CaO, ZnO, BaO, Al_2O_3, K_2CO_3), региоселективно приводящее к 2-этинилпирролам, 2-этинил-4,5,6,7-тетрагидроиндолам или 3-этнилиндолам. Реакции протекают при комнатной температуре и без растворителя. Выходы продуктов этинилирования составляют 60–70 %, а в некоторых случаях достигают 90–94 %. Библиогр. 35 назв. Табл. 1.

Ключевые слова: кросс-сочетание, галогенацетилены, галогенопропионаты, индолы, пирроллы, оксиды металлов и соли, 2-ацилэтинилпирролы, этил 3-(4,5,6,7-тетрагидроиндол-2-ил)-2-пропионты.

The steady interest in pyrrole chemistry is owing, first of all, to the fact that the pyrrole moiety constitutes a core of numerous biologically important compounds such as chlorophyll, hemoglobin, vitamin B12, alkaloids, etc. participating in biotransformation of solar energy, oxygen transfer processes and other life-sustaining reactions [1, 2].

Currently, pyrroles, including functionally substituted ones, are intensively employed in the synthesis of natural compound congeners [3], as pharmacophores [4–7] and building blocks for drug design. For example, anticancer antibiotic CC-1065 [8, 9] incorporates the pyrrole fragment in its structure. The Lipitor (Atorvastatin), one of the best selling drugs in pharmaceutical history used for lowering blood cholesterol, represents functionalized 2,3-diphenylpyrrole [10, 11].

Functionalized pyrroles draw attention as molecular optical switches (including superfast ones) for design of photo- and electroconducting devices, micro- and nanomachines [12–14], and also as ligands for new photocatalysts and synthetic biologically active complexes [15].

In this line, functionalization of pyrroles represents an urgent challenge. Among universal types of reactive carriers of the pyrrole moiety, suitable for various purposes of organic synthesis, are their ethynyl derivatives. In the pyrrole nucleus, the presence of acetylene function, which is sensitive towards nucleophilic, radical and electrophilic attacks as well

as to cycloaddition and polymerization, defines importance of these compounds as highly reactive multi-faceted building blocks.

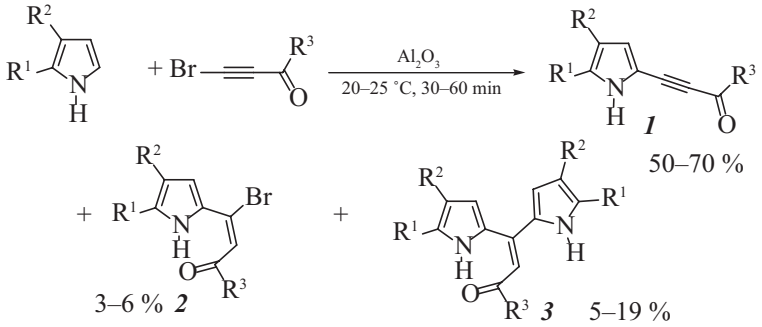
Therefore a great deal of research efforts is invested in the development of efficient methods for the synthesis of ethynylpyrroles, especially those bearing strong acceptor substituents at the triple bond.

The interest in such acetylenes is obvious: the strong electron-acceptor at the triple bond dramatically increases its electrophilicity that allows performing the reaction of nucleophilic addition (typical for acetylenes) under very mild conditions, often quantitatively and stereoselectively, without catalysts and superbase reagents.

However introduction of such activated acetylenic substituents into the pyrrole scaffold remained until recently a stubborn problem since the known methods (for example, Sonogashira reaction [16–19]) were limited by the synthesis of acetylenes containing donor functionalities only. Besides, almost all common methods for ethynylation of the pyrrole ring require its preliminary functionalization, mainly with halogens.

In 2004 we have developed [20–22] a fundamentally new method for direct regioselective introduction of acetylenic substituents in the position 2 of the pyrrole ring or position 3 of the indole moiety. The method comprises the reaction of pyrroles or indoles with electron-deficient haloacetylenes on the surface of aluminum oxide.

Thus pyrroles readily react with acylbromoacetylenes on the surface of aluminium oxide to afford 2-(acylethynyl)pyrroles ***1*** (Scheme (1)) [20–22].

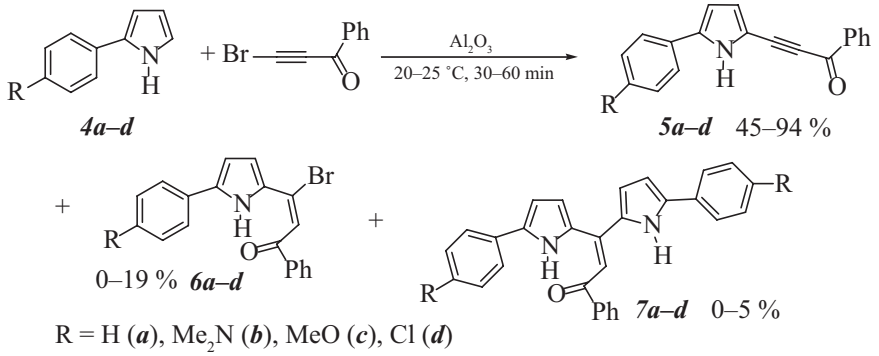


(1)

The reaction occurs at room temperature and is slightly exothermic. It is entirely regioselective: even impurities of isomeric 1- or 3-(acylethynyl)pyrroles are not detected in the reaction mixture. Ethynylation proceeds via the addition of pyrroles to the triple bond of haloacetylene to deliver bromoethenylpyrroles ***2***, which are isolated in small amounts. Pyrroles ***2*** are *E*-isomers with *cis*-orientation towards the position of the carbonyl group and olefinic bond. Such conformation leads to intramolecular hydrogen bonding of NH proton with oxygen atom of the carbonyl function that stabilizes this isomer. This is why this isomer can be isolated. Side products, dipyrrolylethenes ***3***, are likely formed via the substitution of bromine atom in bromoethenylpyrroles ***2***, since pyrroles themselves do not add to ethynylpyrroles under the reaction conditions. The yields of dipyrrolylethenes ***3*** usually do not exceed 20 %, but when pyrroles are used in two-fold molar excess, the yields can reach 40 %.

The question arises of whether ethynylpyrroles are really formed due to elimination of HBr molecule from the primary adducts of the reaction, bromoethenylpyrroles. To answer this question, we have performed ^{1}H NMR monitoring of the reactions between 2-arylpyrroles ***4a–d*** and benzoylbromoacetylene (Scheme (2)) [23]. It is found that the reactions give

ethynyl- (***5a–d***) and bromoethenylpyrroles ***6a–d*** in a ratio, which changes insignificantly with time (Table 1).



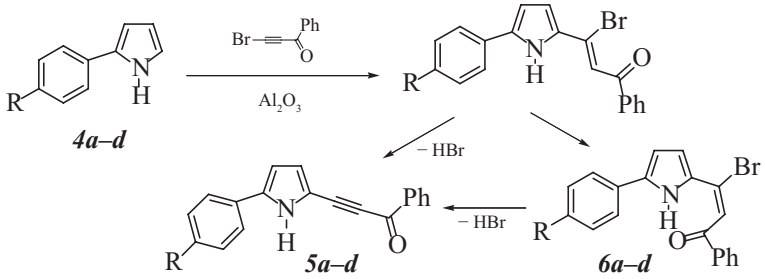
(2)

R = H (***a***), Me_2N (***b***), MeO (***c***), Cl (***d***)

^{1}H NMR monitoring of the reaction between 2-arylpyrroles *4a–d* with benzoylbromoacetylene

R	Reaction time, min					
	10		30		60	
	Composition of the reaction mixture, % (yield, %)					
	5	***6***	***5***	***6***	***5***	***6***
H	75	25	74	26	78	22
Me_2N	51	traces	64	traces	70	traces
MeO	53	17	59	19	64	22
Cl	72	18	79	21	81 (94)	19 (3)

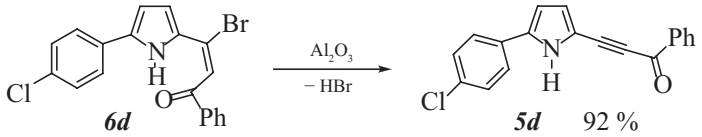
Apparently, the constant ratio of these products can be rationalized as follows. The pyrroles add to acetylene according to the rule of trans-nucleophilic addition to deliver *Z*-isomers of bromoethenylpyrroles ***6a–d***. The latter partially eliminate HBr giving ethynylpyrroles ***5a–d***, and partially isomerize into the *E*-isomers stabilized by strong intramolecular bonding (Scheme (3)). Since *cis*-elimination proceeds slower than *trans*-elimination, a certain amount of *E*-bromoethenylpyrroles ***6a–d*** remains in the reaction mixture.



(3)

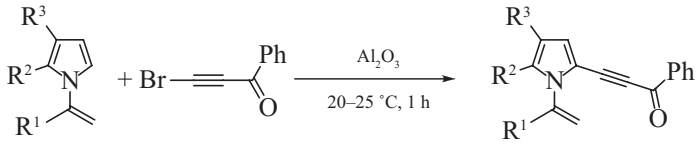
The fact that ethynylpyrroles ***5a–d*** are formed from bromoethenylpyrroles ***6a–d*** can be confirmed by comparison of their concentration in the reaction mixture with isolated yields. During the purification by column chromatography on aluminum oxide, the reaction continues giving ethynylpyrroles ***5a–d*** in higher yields and bromoethenylpyrroles ***6a–d*** in lower yields. Besides, one should bear in mind that preliminarily isolated 2-(1-bromo-2-benzoylethenyl)-5-(4-chlorophenyl)pyrrole (***6d***) is easily transformed to the corresponding

ethynylpyrrole ***5d*** (Scheme (4)). All this confirms that bromides ***6a–d*** are intermediate products of the cross-coupling.



(4)

Unlike NH-pyrroles, the interaction of 1-vinyl- (***7a–c***) and 1-isopropenylpyrroles ***8a–c*** with benzoylbromoacetylene on aluminum oxide exclusively affords the cross-coupling products ***9a–c***, ***10a–c*** (Scheme (5)) [24]. In this case, neither dipyrrolylethenes nor the reaction intermediates (bromoethenylpyrroles) are detected. Probably, the latter are not found in the reaction mixture due to the lack of possibility of their stabilization by intramolecular hydrogen bonding.



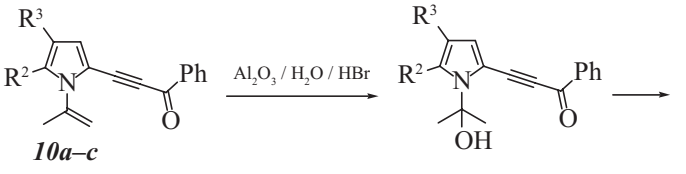
7a–c, 8a–c ***9a–c, 10a–c***

R^1 = H (***7, 9***), Me (***8, 10***); R^2 = R^3 = H (***a***)
R^2 = Ph, R^3 = H (***b***); R^2–R^3 = $(CH_2)_4$ (***c***)

42–70 %

(5)

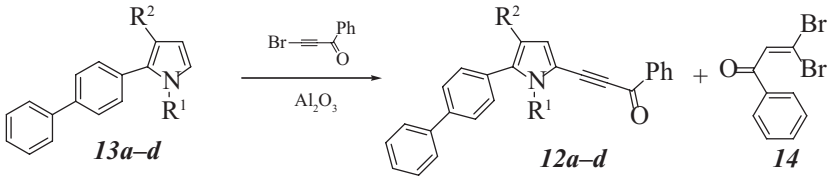
1*H*-2-(Benzoylethynyl)pyrroles ***6a***, ***11a, b*** are isolated as side-products of 1-isopropenylpyrroles ***8a–c*** ethynylation. They are likely formed owing to hydrolysis of the isopropenyl group of ethynylpyrroles catalyzed by eliminating HBr since hydrate water is always present in Al_2O_3 (Scheme (6)).



(6)

R^2 = R^3 = H (***11a***)
R^2 = Ph, R^3 = H (***6a***); R^2–R^3 = $(CH_2)_4$ (***11b***)

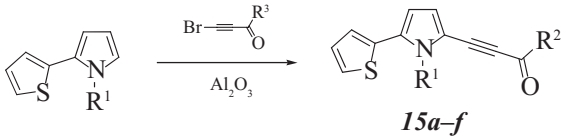
There is another example of the pyrrole ring ethynylation with benzoylbromoacetylene in the presence of aluminum oxide. The corresponding 2-benzoylethynyl-5-(1,1-diphenyl)pyrroles ***12a–d*** are synthesized in 35–46 % yields from 2-(1, 1′-diphenyl-4-yl)pyrroles ***13a, b*** and their 1-vinyl derivatives ***13c, d*** (Scheme (7)) [25]. In this case, the reaction proceeds slower than with 2-phenylpyrrole. A side product of the reaction is dibromophenylpropenone ***14***, an adduct of bromobenzoylacetylene with HBr, which is released upon ethynylation.



13a–d *12a–d* *14* (7)

R^1 = H; R^2 = H (***a***), Ph (***b***)
R^1 = CH=CH_2; R^2 = H (***c***), Ph (***d***)

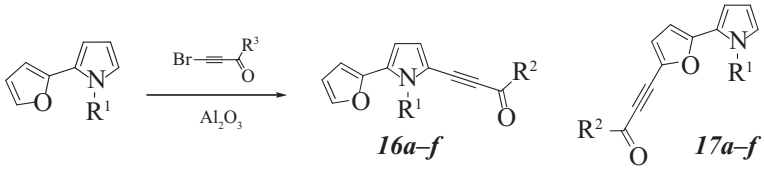
The reaction of 2-(2-furyl)- and 2-(2-thienyl)pyrroles with acylbromoacetylenes is of special interest. The presence of two five-membered aromatic rings capable of ethynylation equivocate outcome of these. It appears that in the case of 1*H*- and 1-vinyl-2-(2-thienyl)pyrroles, the reaction proceeds selectively to deliver 2-(2-thienyl)pyrroles ***15a–f*** bearing acetylenic substituents in the pyrrole ring (Scheme (8)).



15a–f (8)

R^1 = H; R^2 = Ph (***a***), 2-furyl (***b***), 2-thienyl (***c***)
R^1 = CH=CH_2; R^2 = Ph (***d***), 2-furyl (***e***), 2-thienyl (***f***)

Under these conditions, 2-(2-furyl)pyrrole and its N-vinyl derivative react in other fashion: along with the main direction of the reaction (ethynylation of the pyrrole ring), the attack of α-position of the furan moiety at the triple bond takes place (Scheme (9)). The ratio of ethynylation products across the pyrrole (***16a–f***) and furan (***17a–f***) cycles is ≈ 5 : 1 (^{1}H NMR).

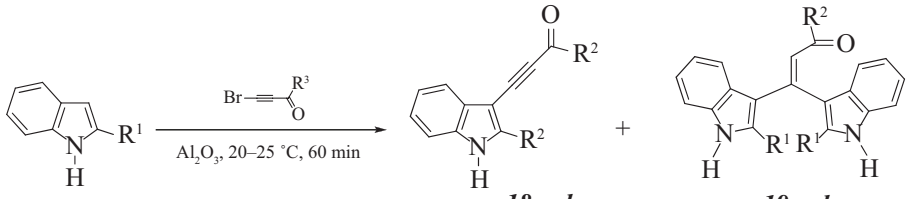


16a–f ***17a–f*** (9)

R^1 = H; R^2 = Ph (***a***), 2-furyl (***b***), 2-thienyl (***c***)
R^1 = CH=CH_2; R^2 = Ph (***d***), 2-furyl (***e***), 2-thienyl (***f***)

The results obtained can be considered as a discovery of new reaction of direct palladium-free ethynylation of the furan ring with functional haloacetylenes.

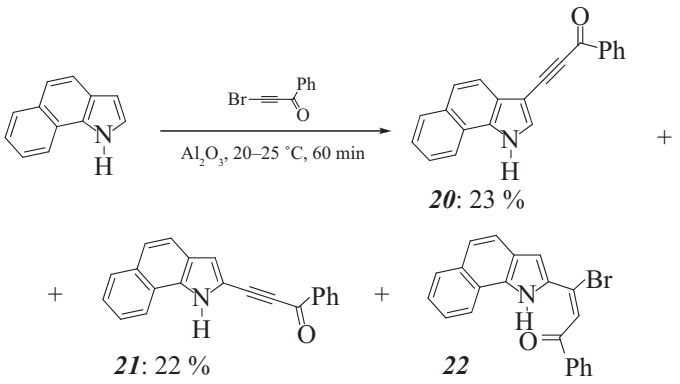
Indole and 2-methylindole smoothly react with benzoylbromoacetylene on the surface of aluminum oxide to furnish 3-benzoylethynylindoles ***18a, b*** (R = Ph, Scheme (10)) [26]. It is the first example of the indole nucleus direct ethynylation. Without aluminum oxide, as in the case of pyrroles, the ethynylation does not take place. The only side-products, diindolylethenes, are formed in negligible amounts. With bromopropynoate, the corresponding ethynylation products ***18c, d*** (R^2 = OEt, Scheme (10)) are produced in 17 % and 12 % yields [27].



18a–d 19a–d (10)

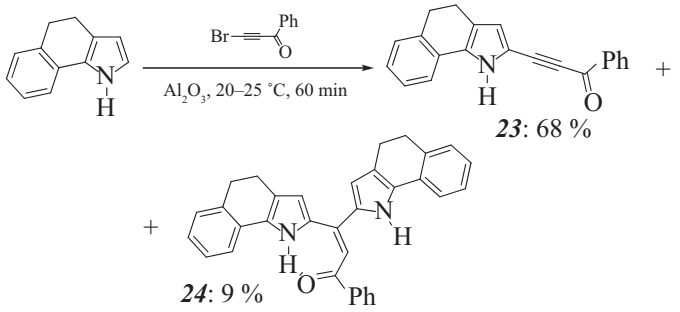
R^2 = Ph: R^1 = H (***a***), Me (***b***)
R^2 = OEt: R^1 = H (***c***), Me (***d***)

The reaction of a fused indole, benz[g]indole, with benzoylbromoacetylene under the same conditions gives a mixture of 3- (***20***) and 2-ethynylindoles ***21*** in 45 % total yield (Scheme (11)) [26]. In this case, the reaction mixture contains also *E*-isomer of 2-bromoethenylbenz[g]indole ***22*** stabilized by intramolecular hydrogen bonding.



(11)

4,5-Dihydrobenz[g]indole, which is a pyrrole by nature, readily reacts with benzoylbromoacetylene in the presence of aluminum oxide to afford 2-ethynylpyrrole ***23*** (Scheme (12)) [26]. Dipyrrolylethene ***24*** is isolated from the reaction mixture in 9 % yield [26].

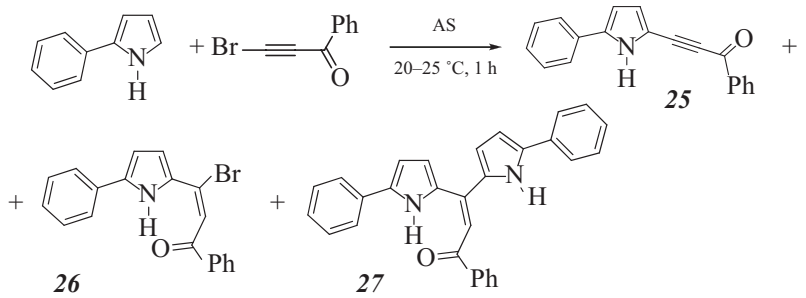


(12)

Thus, we have shown that pyrrole and indoles are easily ethynylated with haloacetylenes on the surface of aluminum oxide.

This brings up another question, whether aluminum oxide is a unique active surface for implementation of the cross-combination or other oxides and salts can also promote this reaction. To answer this question, we have investigated the interaction of 2-phenylpyrrole with benzoylbromoacetylene in the presence of metal oxides (ZnO, BaO, Al_2O_3, MgO, CaO, TiO_2, ZrO_2) without solvent [28]. It turns out that this reaction, depending on the active

surface, leads to either cross-coupling product ***25*** or 2-phenylpyrrole adduct to acetylene triple bond (compound ***26***) (Scheme (13)). Activity of metal oxides in the ethynylation reaction drops as follows: ZnO (81 %), BaO (73 %), Al_2O_3 (71 %), MgO (69 %), CaO (50 %) (in brackets, the content of benzoylethynylpyrrole ***25*** in the reaction mixture is given).

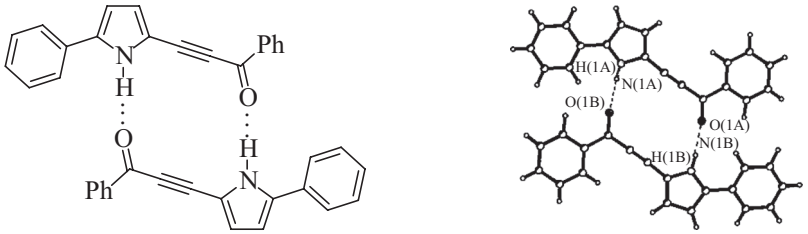


(13)

AS = MgO, CaO, BaO, Al_2O_3, SiO_2, TiO_2, ZrO_2, $CaCO_3$, $ZrSiO_4$

Like on aluminum oxide, the cross-coupling on these surfaces is accompanied by formation of insignificant amounts of bromoethenylpyrrole ***26*** and dipyrrolylethene ***27***.

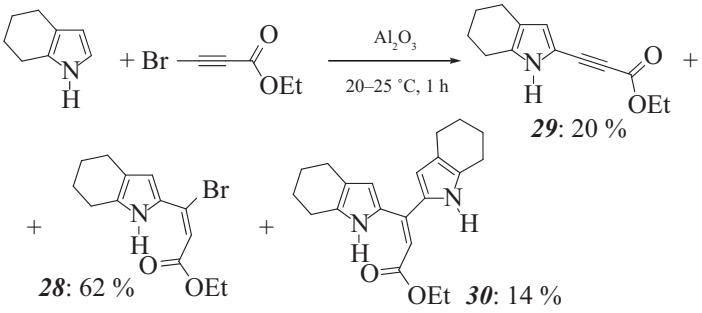
Titanium, zirconium and silicon [29] dioxides, inactive in the cross-coupling, are specific catalysts of regio- and stereoselective addition of pyrroles to the triple bond of benzoylbromoacetylene giving rise to bromoethenylpyrrole ***26***. The latter is prepared and purified on zirconium oxide in 60 % yield [28]. When purification is performed on aluminum oxide, only ethynylpyrrole ***25*** is formed, and it crystallizes exclusively as a rotamer with a *cis*-configuration of the NH and CO groups [28]. Meanwhile, 2-benzoylethynyl-5-phenylpyrrole, obtained from 2-phenylpyrrole and benzoylbromoacetylene on the surface of aluminum oxide, gives two crystalline modifications with the carbonyl group oriented toward *cis*- and *trans*-position relative to the nitrogen atom [30]. In this case, isolation of ethynylpyrrole ***25*** mainly as *cis*-rotamer is likely explained by Al_2O_3-induced *cis*-elimination of HBr from *E*-isomer of bromoethenylpyrrole ***26*** with instant stabilization of *cis*-oriented N−H and C=O bonds to the macrocyclic dimer (Scheme (14))



(14)

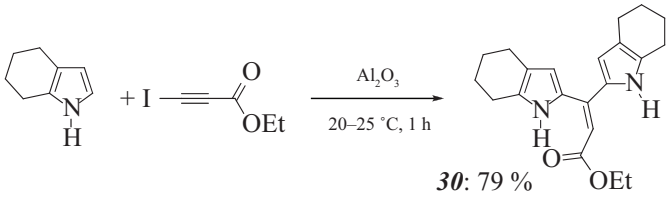
Thus, the cross-coupling of pyrroles with acylbromoacetylenes in the presence of aluminum oxide leads mainly to acylethynylpyrroles. The reactions of pyrroles with chloro- and iodobenzoylacetylenes proceed under these conditions in a similar fashion. Only the reaction rate changes, while its direction remains intact: in this case, nature of the halogen at the triple bond does not influence the process course.

Under close conditions, bromopropynoate reacts with a tetrahydroindole to furnish bromopropenoate ***28*** as a major product (Scheme (15)) [31]. When aluminum oxide is used in 50-fold excess, the only reaction products are tetrahydroindolylpropynoate ***29*** and ditetrahydroindolylacrylate ***30***, the latter being prevailing. The yield of tetrahydroindolylpropynoate ***29*** increases up to 58 %, when 10 % potassium carbonate is added to aluminum oxide.



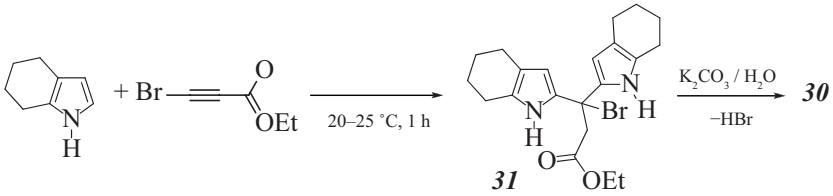
(15)

Unlike bromopropynoate, iodopropynoate reacts with tetrahydroindole on the surface of aluminum oxide (used both in 10-fold and 50-fold excess) of various basicity to exclusively form ditetrahydroindolylacrylate ***30*** (Scheme (16)) [31].



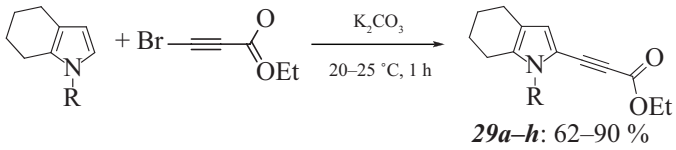
(16)

Tetrahydroindole reacts with bromopropynoate without aluminum oxide and solvent to give unstable ditetrahydroindolylbromoethane ***31*** (Scheme (17)). The latter is treated in chloroform with aqueous K_2CO_3 followed by elimination of HBr and formation of product ***30***.



(17)

It has been shown [31] that the addition of potassium carbonate to aluminum oxide results in the increase of ethynylpyrrole yields. What will happen if pure potassium carbonate is employed as solid surface? It turns out that in this case both tetrahydroindole and its N-substituted derivatives are ethynylated selectively to deliver the corresponding ethynyl derivatives ***29*** in up to 90 % yields (Scheme (18)) [32].



(18)

R = H (***a***), Me (***b***), Bn (***c***), CH=CH_2 (***d***), *i*-Pr(CH)CH_3 (***e***), *n*-Bu(CH)CH_3 (***f***), $(CH_2)_2$SEt (***g***), $(CH_2)_2$SPr-*n* (***h***)

In the case of bromopropynoate, no side products are detected. Iodopropynoate also selectively react with tetrahydroindole on aluminum oxide to exclusively afford tetrahydroindolylpropynoate ***29a***. The content of acrylate ***30a*** in this case is only 2–4 %. In

solvents (diethyl ether, chloroform) this reaction does not proceed either with or without K_2CO_3. Regioselectivity of the ethynylation is not violated even by such bulky substituents as CH(Me)OPr-*i* and CH(Me)OBu-*n*, though the reaction time considerably increases (12 h instead of 1 h) and portion-wise addition of bromopropynoate to the reaction mixture is required. Obviously, the low reaction rate is due to steric shielding of the pyrrole ring position 2 by a substituent.

Thus, we have discovered and now successfully develop the new cross-coupling of pyrroles and indoles with haloacetylenes. The reaction is carried out under mild conditions on solid surfaces of metal oxides and salts, without palladium, copper and solvents. Besides, preliminary functionalization of the pyrrole ring is not required. This cross-coupling essentially complements the available methods of ethynylpyrrole synthesis (including Sonogashira reaction), which do not allow to introduce acetylenic fragments having strong electron-withdrawing substituents into the pyrrole or indole ring, and employ unstable halogenated pyrroles or indoles as starting reagents. The potential of this new cross-coupling is still far from to be exhausted: one can assume that it will tolerate not only halogenated acylacetylenes and propynoates, but also acetylenes with other electron-withdrawing substituents such as sulfonylacetylenes, acetylenecarboxylic acid amides, trifluoromethyl and trifluoroacetyl derivative, etc.

From the moment of its discovery, this reaction arrested the attention and now is cited not only in research papers [33], but also in reviews [34] and monographs [35]. Most often this reaction is referred to as inverse Sonogashira coupling. Though this term was originally proposed by us [20], we do not consider it as good choice, since the chemical essence of such ethynylation has nothing to do with palladium-catalyzed Sonogashira cross-coupling.

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