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PII: S0040-4039(15)01253-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.07.078
Reference: TETL 46567

To appear in: *Tetrahedron Letters*

Received Date: 9 June 2015
Revised Date: 15 July 2015
Accepted Date: 29 July 2015

Please cite this article as: Politanskaya, L., Shteingarts, V., Tretyakov, E., Potapov, A., The *p*-toluenesulfonic acid-catalyzed transformation of polyfluorinated 2-alkynylanilines to 2-aminoarylketones and indoles, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.07.078

Tetrahedron Letters
journal homepage: www.elsevier.com

# The *p*-toluenesulfonic acid-catalyzed transformation of polyfluorinated 2-alkynylanilines to 2-aminoarylketones and indoles

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
*p*-TSA–catalyzed hydration
Polyfluorinated 2-alkynylanilines
Polyfluorinated 2-aminoarylketones
Polyfluorinated indoles

ABSTRACT

The reactivity of a series of polyfluorinated 2-alkynylanilines with various alcohols using *p*-TSA has been studied. It was found that hydration of the triple bond gave rise to polyfluorinated 2-aminoarylketones and competed with an electrophilic heterocyclization reaction leading to polyfluorinated indoles. The dependence of the reaction pathways on the nature of the alkynylaniline substituents has been examined.



The catalyzed addition of water to alkynes (hydration) is one of the most convenient methods to construct a carbon-oxygen bond and generate valuable carbonyl compounds with high atom economy.[1] There are several different synthetic protocols for triple bond hydration. The mercury(II) assisted hydration of alkynes, first described by Kucherov,[2] has become one of the classical synthetic procedures. In recent years, with increasing demand for the use of less toxic metal catalysts, new methods for alkyne hydration have been developed including those catalyzed by Au–$PPh_2$–PMO(Ph) (PMO – periodic mesoporous organosilicas),[3] cobalt(III) porphyrin complexes,[4] Pd(II)–$CuCl_2$–$O_2$,[5] Sn/HCl(aq),[6] and $SnCl_2$.[7] At the same time, alternative metal-free protocols have been disclosed based on the use of Brønsted acids such as HCl,[8] $H_2SO_4$,[9] $HCO_2H$,[10–12] MsOH,[13] TfOH or $Tf_2NH$,[14] and *p*-TSA.[15] The use of *p*-TSA is perhaps the most attractive, as it was reported[16,17] that substituted alkynes in aqueous or alcohol solvents underwent hydration to afford carbonyl compounds in good to excellent yields. This procedure, which afforded only Markovnikov adducts, is characterized by the mildness of the acidic conditions and excellent regio– and chemoselectivity. For these reasons, *p*-TSA was chosen for the hydration of a previously obtained[18] series of polyfluorinated 2-alkynylanilines. This series was thought to be interesting, because, on the one hand, accumulation of electron-withdrawing fluorine atoms on the aromatic ring should prevent hydration, especially in case of benzo-perfluorinated *o*-alkynylanilines. On the other hand, the presence of the electron-donating amino group on the *o*-position of the aromatic ring may compensate for the effect of these acceptors. Finally, there is scarce evidence that *o*-alkynylanilines undergo acid-catalysed cyclization to form indoles.[21] It has also been reported[17] that, contrary to other substrates, diarylalkynes containing a methoxy– or thiomethyl substituent at the *o*-position in the presence of *p*-TSA do not produce arylketones and instead undergo electrophilic cyclization to produce benzofuran and benzothiophene derivatives. Therefore, it is difficult to predict the result of the conversion of polyfluorinated 2-alkynylanilines in an acidic medium.

Thus, the aim of the present work was to examine the reactivity of benzo-polyfluorinated 2-alkynylanilines in various alcohols using *p*-TSA.

Previously reported polyfluorinated 2-iodoanilines **1(a–e)**[18] were cross-coupled with terminal alkynes **2(a–c)** to give the required polyfluorinated *o*-alkynylanilines **3(a–e)(a–c)**.[18] The crude products **3** were heated at reflux in various alcohols in the presence of *p*-TSA (Scheme 1). To optimize the reaction conditions, a large series of experiments were carried out in which the solvent, catalyst loading and reaction time were sequentially varied for each substrate. In each case, the reaction was terminated after $^{19}F$ NMR signals belonging to the starting compounds had completely disappeared. The data on the optimized experimental conditions and the yields of the products formed are summarized in Table 1.

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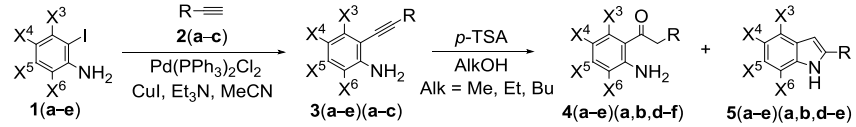
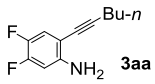
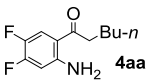
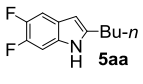
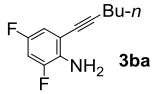
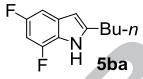
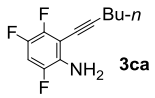
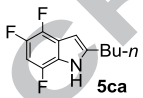
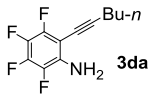
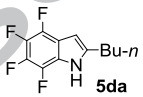
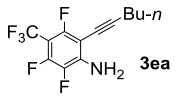
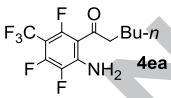
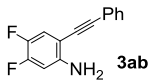
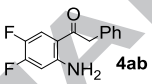
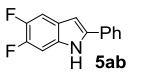
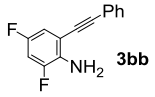
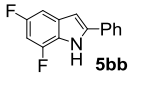
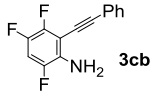
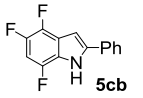
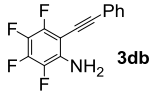
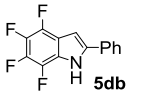
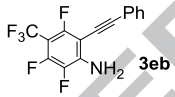
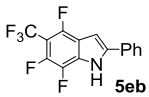
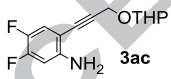
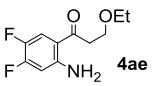
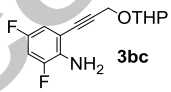
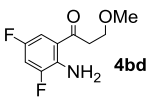
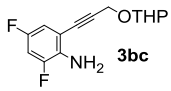
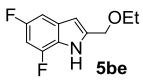
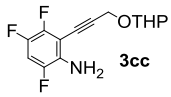
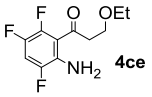
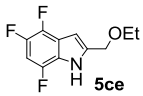
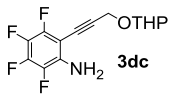
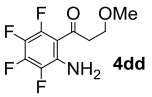
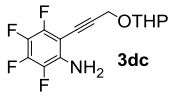
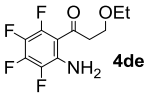
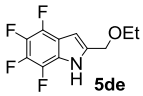
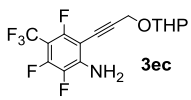
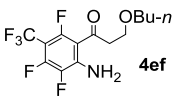



**Scheme 1.** Synthesis of polyfluorinated 2-aminoarylketones **4** and indoles **5**.

**Table 1.** The *p*-TSA–catalyzed transformation of 2-alkynylanilines **3** into 2-aminoarylketones **4** and indoles **5** in AlkOH[a]

| Entry | Substrate | *p*-TSA (equiv) | AlkOH, Alk = | Time (h) | Product Ketone | Yield[b] (%) | Product Indole | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 |  **3aa** | 2 | Et | 7 |  **4aa** | 60 |  **5aa** | 12 |
| 2 |  **3ba** | 2 | Et | 5 | | |  **5ba** | 62 |
| 3 |  **3ca** | 2 | Et | 12 | | |  **5ca** | 48 |
| 4 |  **3da** | 2 | Et | 33 | | |  **5da** | 57 |
| 5 |  **3ea** | 2 | Bu | 23 |  **4ea** | 52 | | |
| 6 |  **3ab** | 1 | Et | 8 |  **4ab** | 32 |  **5ab** | 13 |
| 7 |  **3bb** | 2 | Et | 20 | | |  **5bb** | 30 |
| 8 |  **3cb** | 2 | Me | 16 | | |  **5cb** | 67 |
| 9 |  **3db** | 2 | Et | 7 | | |  **5db** | 56 |
| 10 |  **3eb** | 2 | Bu | 20 | | |  **5eb** | 64 |
| 11 |  **3ac** | 2 | Et | 6 |  **4ae** | 25 | | |
| 12 |  **3bc** | 1 | Me | 20 |  **4bd** | 62 | | |
| 13 |  **3bc** | 2 | Et | 5 | | |  **5be** | 27 |
| 14 |  **3cc** | 5 | Et | 62 |  **4ce** | 6 |  **5ce** | 45 |
| 15 |  **3dc** | 2 | Me | 40 |  **4dd** | 31 | | |
| 16 |  **3dc** | 2 | Et | 20 |  **4de** | 54 |  **5de** | 14 |
| 17 |  **3ec** | 2 | Bu | 8 |  **4ef** | 78 | | |

[a] Reaction conditions: 2-alkynylanilines **3** (2 mmol), *p*-TSA (2–10 mmol), AlkOH (25 mL), reflux.

[b] Isolated yield over 2 steps from iodoanilines **1**(**a**–**e**).

Depending on the reaction conditions, arrangement and number of fluorine atoms on the aromatic ring, the *p*-TSA–catalyzed conversion of *o*-alkynylanilines **3** led to the formation of 2-aminoarylketones **4**, indoles **5** or a mixture of these two compounds. The reaction of compounds **3a(a–c)**, containing two fluorine atoms in *p*-positions relative to the amino and acetylene groups in EtOH, produced either a mixture of indoles **5a**(**a**,**b**) and ketones **4a**(**a**,**b**) which predominantly contained the latter compound or solely the corresponding ketone **4ae** (Entries 1, 6, 11). The reaction of **3ac** was accompanied by a noticeable thickening of the reaction mixture, and despite the fact that ketone **4ae** was the only product, its yield was low (Entries 11). Deprotection of the THP–protecting group is known to proceed easily even at room temperature,[19] and it is reasonable to assume that in the case of **3ac** (and all related compounds), hydration of the triple bond was accompanied by alcoholysis of the $CH_2OTHP$ fragment.

The isomeric *o*-alkynylanilines **3b**(**a–c**), in which both fluorine atoms were in a *m*-position relative to the acetylene group gave only fluorinated indoles **5b**(**a**,**b**,**e**) (Entries 2, 7, 13). Notably, in the case of compound **3bc**, the reactivity toward triple bond hydration was altered by carrying out the reaction in MeOH (Entry 12) leading to the selective formation of ketone **4bd** in 62% yield. In contrast, the reaction of **3ba** in MeOH was very slow and only 10% of the corresponding carbonyl compound (which could not be isolated) was observed in the reaction mixture after 15 h. When the reaction of **3bb** was conducted in MeOH, after 40 h the conversion of the starting compound was approximately 50% and the reaction product in this case was indole **5bb**. Thus, in the cases of *o*-alkynylanilines **3ba** and **3bc**, the rates of acid–catalyzed triple bond hydration and heterocyclisation could be altered in favor of preferential formation of the carbonyl compounds using MeOH instead of EtOH.

However, for the trifluoro-substituted compounds **3c(a–c)** containing a fluorine atom in the *o*-position relative to the acetylene group, the reaction was always in favor of heterocyclization, even when performing the reaction in MeOH (Entries 3, 8, 14). Moreover, the accumulation of the deactivating effect of the fluorine atoms was responsible for a significant increase of the time required for reaction completion: 62 h in the case **3cc** even when using 2.5 times more catalyst.

The reaction time was significantly reduced by the introduction of a fourth fluorine atom in the *p*-position relative to the acetylene group (Entry 16) in spite of a lower amount of catalyst when compared to Entry 14. It is noteworthy that the predominant reaction product in this case was ketone **4de**. Indole formation was not observed when the same reaction was carried out in MeOH (Entry 15), however the yield of the corresponding ketone **4dd** was significantly reduced in comparison to the yield of ketone **4de** (Entry 16) due to thickening of the reaction mixture. Interestingly, other tetrafluoro-substituted substrates **3d**(**a**,**b**) gave only the heterocyclisation products in good yields (Entries 4, 9). The marked tendency of the highly deactivated substrates containing the $CH_2OTHP$-group (or rather the $CH_2OAlk$–group, formed *in situ*) to form carbonyl compounds was most apparent in the case of compound **3ec** (Entry 17). This compound possessed low reactivity and, therefore, remained unchanged at reflux in MeOH and EtOH in presence of *p*-TSA. However, using more forcing conditions (boiling BuOH) gave ketone **4ef** in 78% yield. *o*-Alkynylaniline **3ea**, bearing an alkyl substituent at the triple bond reacted similarly, to form the corresponding ketone (Entry 5). However, in the case of the related phenyl–substituted substrate **3eb**, only indole **5eb** was formed in approximately the same yield (Entry 10).

Thus, the main conclusion of our work was that the highly deactivated polyfluorinated *o*-alkynylanilines could successfully be involved in acid–catalyzed transformations. Particular sets of fluorine substituents on the aromatic ring, regioselectively provide the triple bond hydration products. Especially in this regard, alkynes **3(a–e)c** with $R = CH_2OTHP$ stand out as they appear to be more prone to the *p*-TSA–catalyzed hydration reaction than other substrates. Generally, in the case of substrates with R = Bu and Ph, the content of the ketone formed decreased or vanished completely and only the corresponding indole was formed. According to Table 1, taking into account the product ratio of **4**/**5**, it can be seen that the activating towards hydration effect of R decreases in the series ($CH_2OAlk > Bu \geq Ph$) for a given set of substituents on the aromatic ring.

Analysis of the influence of the location and number of fluorine atoms on the product ratio of **4**/**5** revealed the following general trends. The replacement of a *p*-hydrogen atom relative to the triple bond on a fluorine atom increased the ability of the alkynylanilines to undergo hydration (compare Entries 2 (**4**/**5** = 0/62) and 1 (**4**/**5** = 60/12), 13 (**4**/**5** = 0/27) and 11 (**4**/**5** = 25/0), 14 (**4**/**5** = 6/45) and 16 (**4**/**5** = 54/14)). This could be easily explained by the fluorine atom being a π-donating substituent. As for the other positions on the aromatic ring, a cumulative effect of fluorine atoms was present. The acceptor influence of the substituents on the alkynylaniline increases as the number of fluorine atoms increases, and this effect prevents the hydration reaction. In terms of the influence of the number of fluorine atoms on the preference for the formation of the carbonyl compounds, rather than the cyclization products, the substrates can be arranged in the following order (Figure 1).

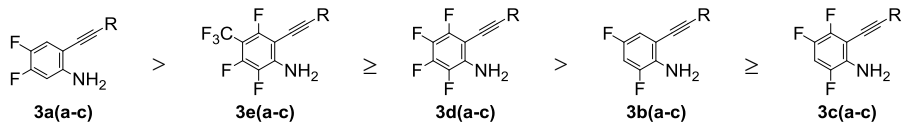
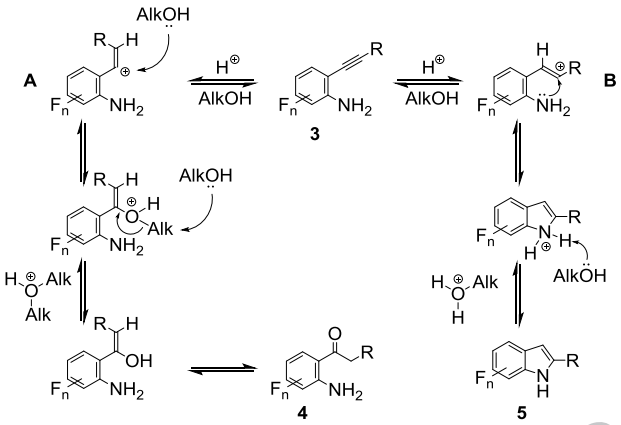



**Figure 1.** Relative reactivity of alkynylaniline to the *p*-TSA–catalyzed hydration reaction.

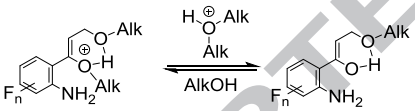
The proposed mechanism for the formation of 2-aminoarylketones **4** and indoles **5** is shown in Scheme 2. Initially, protonation of alkynylaniline **3** gives the intermediate cations **A** and **B**. The relative stability of these carbocations is determined by the ability of the substituents to help stabilize the positive charge. When R is $CH_2OAlk$ or an *n*-Bu–group, formation of **A** is preferred since the vinyl cation intermediate can be stabilized by the fluorinated aromatic ring. Subsequent addition of the alcohol gives an enol, which tautomerizes to its more stabilized keto form **4**. According to this, it can be seen that two alcohol molecules are involved in the conversion of the triple bond into a keto–group. One attacks the vinyl cation to form a substituted oxonium cation, while the other reacts to give the enol. This reaction mechanism helps to explain the fact that in MeOH, alkynylanilines **3** were more prone to the formation of ketones compared to those performed in EtOH. Moreover, the presented scheme helped

elucidate the reasons behind the high propensity for hydration of compounds bearing $CH_2OAlk$–groups. Presumably, these are capable of forming an intramolecular hydrogen bond with the substituted oxonium cation and the hydroxyl group of the enol, which should promote the hydration reaction (Scheme 3).




**Scheme 2.** Proposed mechanism for the acid promoted formation of polyfluorinated 2-aminoarylketones **4** and indoles **5**.

When R is a phenyl group, formation of **B** is preferred, furnishing the five-membered indole. When the total effect of the fluorine atoms and amino–group makes the substituted aniline a stronger donor than the phenyl ring, protonation of the triple bond leads to the formation of intermediate **A** and carbonyl compounds (as was the case for **4ab**). In all other cases, the fluorine atoms led to the substituted aniline becoming less efficient at stabilizing the positive charge than the phenyl ring making formation of **B** preferred, giving rise to indoles **5(b–e)b**. The observed *p*-TSA–catalyzed heterocyclization of the polyfluorinated 2-phenylethynyl-anilines can be considered as a selective approach to benzo-polyfluorinated 2-phenylindoles. The reaction yields are comparable to those obtained by the KOH–promoted cyclization of polyfluorinated 2-alkynylanilines.[19]




**Scheme 3.** Putative intramolecular hydrogen bonds in compounds **4(a–e)(d–f)**.

In summary, the purpose of this study was to expand the applications of the *p*-TSA–catalyzed hydration of arylalkynes using a range of polyfluorinated 2-(alkynyl)anilines prepared by the Sonogashira cross-coupling of the corresponding 2-iodanilines with terminal alkynes. We have demonstrated the formation of polyfluorinated 2-aminoarylketones and / or benzo-polyfluorinated indoles using this reaction.[20] It was found that 2-aminoarylketones were the predominant reaction product when R = $CH_2OTHP$, while in the cases of R = *n*-Bu and Ph, indoles were obtained as the main products. The effect of the substituent on the triple bond was a more important factor in determining the path of the reaction, than the fluorine atoms on the aniline ring. A related phenomenon was observed in the acid–catalyzed transformation of 1-(2-(phenylethynyl)phenyl)-urea[21] where in the presence of trifluoromethanesulfonic acid, urea derivatives gave indoles, while use of weaker TFA resulted in protonation of the other carbon atom of the triple bond to ultimately give the six-membered quinazolinone.

Since the polyfluorinated indole nucleus is a structural component in a large number of biologically active compounds, as well as pharmaceuticals,[22] the benzo-polyfluorinated indoles prepared have potential application in terms of their bioactivity.

## Acknowledgments

Analytical and spectral measurements were performed by the Collective Service Center of the Siberian Branch of the Russian Academy of Science. The authors thank the Russian Foundation of Basic Research for financial support (grant 14-03-00108).

**Supplementary Material:** General methods and procedures, assigned $^1H$, $^{19}F$ $^{13}C$ and NMR spectral data in table form, copies of $^1H$, $^{19}F$ and $^{13}C$ NMR spectra. This material is available.

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20. *General procedure*: $Pd(PPh_3)_2Cl_2$ (56 mg, 0.08 mmol), CuI (34 mg, 0.18 mmol) and $Et_3N$ (3 mL) were added to a stirred solution of aniline **1** (2 mmol) and alkyne **2** (3 mmol) in MeCN (12 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at 60 °C for 2 h and allowed to cool to room temperature. Then the mixture was diluted with $CH_2Cl_2$ (10 mL), poured into $H_2O$ (40 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with $H_2O$ (30 mL) and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave the crude product **3** (the $^1H$ and $^{19}F$ NMR spectra closely agreed with the

literature[18]) that was used further without purification. To a solution of crude **3** in alcohol (25 mL), *p*-TSA was added, and the mixture heated at reflux with stirring. The mixture was allowed to cool to room temperature, diluted with $CH_2Cl_2$ (10 mL), poured into $H_2O$ (40 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with $H_2O$ (40 mL) and dried ($MgSO_4$). The solvent was evaporated in *vacuo* to give: a) a mixture of products **4** and **5** that were separated and purified by preparative TLC; b) compound **4** or **5** that was purified by preparative TLC.

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Highlights

- Synthesis of 9 polyfluorinated 2-aminoarylketones and 12 polyfluorinated indoles.
- The *p*-TSA–catalyzed reactions of polyfluorinated 2-alkynylanilines in alcohols.
- Hydration of the triple bond and/or an electrophilic heterocyclization reaction.

## Graphical Abstract

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**The *p*-toluenesulfonic acid-catalyzed transformation of polyfluorinated 2-alkynylanilines to 2-aminoarylketones and indoles**

Larisa Politanskaya, Vitalij Shteingarts, Evgeny Tretyakov and Alexander Potapov