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One-Pot Synthesis of Fluorinated 1-Benzoyl-3,4-dihydroisoquinolines from [2-(*o*-Alkynylphenyl)ethyl]amines by a Hydroamination/Oxidation Sequence

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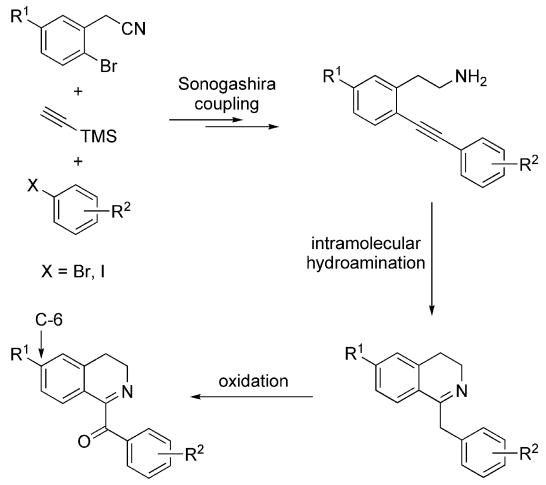
Keywords: Antitumor agents / Nitrogen heterocycles / Hydroamination / Palladium / Oxidation / Titanium

Fluorinated 1-benzoyl-3,4-dihydroisoquinolines can easily be synthesized by a new one-pot procedure from corresponding fluorinated [2-(*o*-alkynylphenyl)ethyl]amines in high yields. The one-pot process consists of an initial [Ind_2TiMe_2]-catalyzed intramolecular alkyne hydroamination and a subsequent Pd-catalyzed oxidation of the benzyl side chain of the resulting hydroamination product. The process tolerates electron-donating and -withdrawing substituents on the benzene ring that is converted into the benzoyl side chain of the products as well as *ortho*-substitution.

Introduction

Benzylisoquinolines are regarded as a class of compounds with a wide range of interesting pharmacological properties, including analgetic, sedative, anesthetic, antitussive, spasmolytic, and sympathomimetic activity.[1] In addition, it was recently reported that a number of 1-benzoyl-3,4-dihydroisoquinolines possess significant antitumor activity at micromolar concentration ($IC_{50} < 5$ μM).[2] While it was found that a hydrophobic group at the C-6 position (e.g. benzyloxy, alkyloxy or allyloxy) seems to be relevant for cytotoxicity,[2] to the best of our knowledge no information is available about the antitumor activity of corresponding 6-fluoro- or 6-trifluoromethyl-substituted or even more halogenated derivatives. At first sight, this is surprising because it is a widely accepted strategy in pharmaceutical research to synthesize fluorinated derivatives of biologically active compounds to improve their pharmacological properties (e.g. metabolic stability and/or lipophilicity).[3] On the other hand, 1-benzoyl-3,4-dihydroisoquinolines are usually synthesized from the corresponding 1-benzyl-3,4-dihydroisoquinolines by selective oxidation of the benzylic carbon[2,4] which means that corresponding fluorinated 1-benzyl-3,4-dihydroisoquinolines are needed as starting materials for the final oxidation step. However, because of the electron-withdrawing nature of the fluoro-substituents these fluorinated imines are not easily accessible by simple electrophilic aromatic substitution reactions (e.g. Bischler–Napieralski reaction).[5]

During the past 10 years we have developed a number of protocols for the catalytic hydroamination of alkenes and alkynes[6–8] which have already been used for the synthesis of biologically interesting target molecules.[9] Based on our initial synthetic strategy towards the enantioselective synthesis of the benzylisoquinoline alkaloid (*S*)-laudanosine[10] we also synthesized a number of norlaudanosine derivatives possessing electron-withdrawing substituents on the benzene ring of the isoquinoline skeleton.[11] In both cases, a Ti-catalyzed intramolecular hydroamination of aminoalkynes (Scheme 1)[12] which takes place in the presence of catalytic amounts of [Cp_2TiMe_2] (Cp = η^5-cyclopentadienyl) or [Ind_2TiMe_2] (Ind = η^5-indenyl) is the key synthetic step. While in the past, the resulting imines were usually reduced to give the envisioned corresponding amine target molecules, we recently decided to directly use the hydroamination products for a subsequent oxidation of the



Scheme 1. Synthetic approach towards the synthesis of fluorinated 1-benzoyl-3,4-dihydroisoquinolines.

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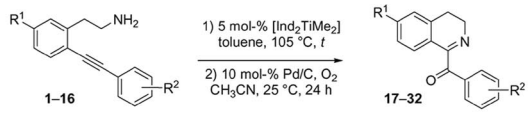
benzylic carbon atom which should lead to the formation of antitumor-active 1-benzoyl-3,4-dihydroisoquinolines. As the result, we now describe a one-pot synthesis of 6-fluoro- and 6-trifluoromethyl-substituted 1-benzoyl-3,4-dihydroisoquinolines from corresponding fluorinated [2-(*o*-alkynylphenyl)ethyl]amines (Scheme 1). An obvious advantage of the envisioned strategy is the fact that these aminoalkynes are easily accessible with high diversity from commercially available starting materials by a Sonogashira-coupling strategy, as described before.[11]

Results and Discussion

Initial experiments were performed with the fluoro-substituted aminoalkyne **1** (Table 1, entry 1) and it was found that the intramolecular hydroamination could easily be achieved in the presence of 5 mol-% [Ind_2TiMe_2] in toluene at 105 °C. In agreement with the accepted mechanism of the Ti-catalyzed hydroamination of alkynes,[8c] the cyclization reaction takes place with complete regioselectivity.[12] After a reaction time of 12 h, it was not possible by TLC analysis to detect the aminoalkyne **1** anymore. The resulting solution of the hydroamination product was then allowed to cool to room temperature and 10 mol-% Pd/C and CH_3CN were added for the subsequent oxidation step.[2] After this mixture had been stirred under an atmosphere of oxygen for 24 h at room temperature TLC analysis showed the formation of a new product which indeed turned out to be the desired 6-fluoro-substituted 1-benzoyl-3,4-dihydroisoquinoline **17**. Final purification by column chromatography gave **17** in 67% yield. In this context it is worth to mention that the oxidation step does not require the use of pure oxygen, it can also be performed in air. However, in this case the rate of the oxidation reaction is significantly reduced and complete conversion is not achieved within 3 days.

Encouraged by this result, we turned our attention towards the synthesis of related 6-fluoro-substituted 1-benzoyl-3,4-dihydroisoquinolines with differently substituted benzoyl side chains. For that reason, the new one-pot procedure was applied to the aminoalkynes **2**–**8** (Table 1, entries 2–8) and it turned out that the process tolerates electron-donating (entries 2, 7) and electron-withdrawing substituents (entries 3, 8) as well as *ortho*-substitution (entries 6–8) of the benzene ring that is converted into the benzoyl side chain. In all cases, the desired keto imines (**18**–**24**) were obtained in good yields (59–77%). Fortunately, quite similar results were obtained during the synthesis of the 6-trifluoromethyl-substituted 1-benzoyl-3,4-dihydroisoquinolines **25**–**32** (Table 1, entries 9–16) from the corresponding aminoalkynes **9**–**16**. Because most of the yields are again good to very good (49–84%) the new one-pot process obviously does not imply any significant limitations with regard to the substituents on the benzene rings of the aminoalkynes. Especially interesting is the fact that even the bis(trifluoromethyl)-substituted products **27** and **32** are obtained in very good yields.

Table 1. One-pot synthesis of fluorinated 1-benzoyl-3,4-dihydroisoquinolines from [2-(*o*-alkynylphenyl)ethyl]amines.



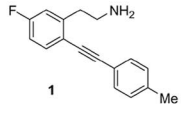
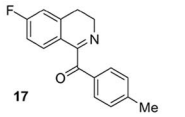
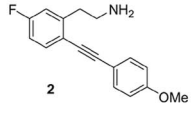
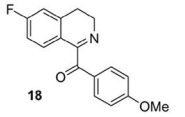
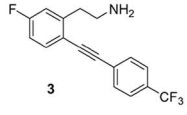
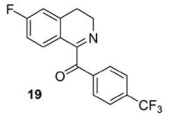
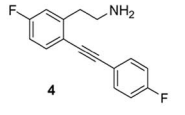
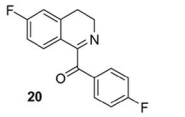
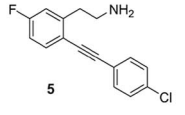
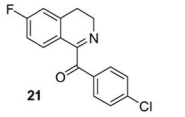
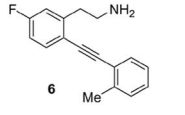
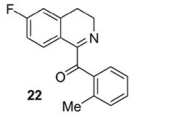
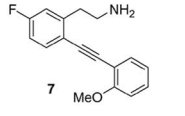
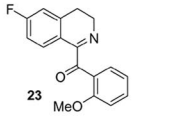
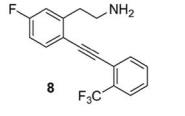
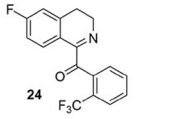
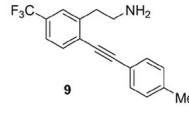
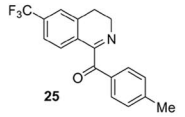
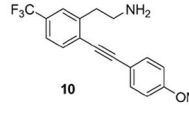
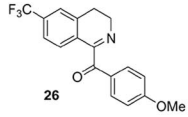
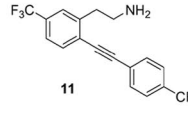
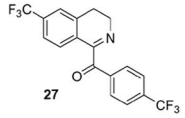
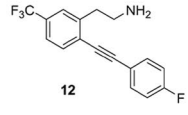
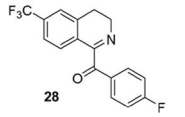
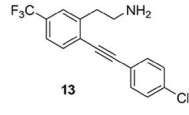
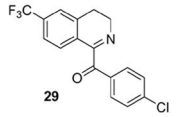
Entry	Alkyne	t [h]	Product	Yield [%][a]
1		12		67
2		16		62
3		16		65
4		12		72
5		16		74
6		14		77
7		16		59
8		15		65
9		12		73
10		16		49
11		16		57
12		16		83
13		16		75

Table 1. *(Continued)*

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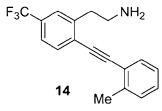
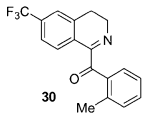
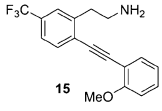
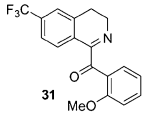
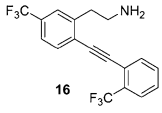
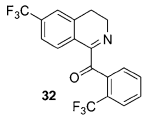
14	 **14**	14	 **30**	84
15	 **15**	16	 **31**	82
16	 **16**	15	 **32**	76

[a] Typical reaction conditions: (a) aminoalkyne (1.00 mmol), [Ind_2TiMe_2] (0.05 mmol, 5 mol-%), toluene (1 mL), 105 °C, 12–16 h; (b) Pd/C (0.10 mmol Pd, 10 mol-%), CH_3CN (3 mL), O_2 (1 atm), 25 °C, 24 h. Yields refer to isolated pure compounds.

Conclusions

In summary, we have shown that potentially antitumor-active fluorinated 1-benzoyl-3,4-dihydroisoquinolines can easily be synthesized by a new one-pot procedure from corresponding fluorinated [2-(*o*-alkynylphenyl)ethyl]amines in high yields. The one-pot process consists of an initial [Ind_2TiMe_2]-catalyzed intramolecular alkyne hydroamination and a subsequent Pd-catalyzed oxidation of the benzyl side chain of the resulting hydroamination product. The process tolerates electron-donating and -withdrawing substituents on the benzene ring that is converted into the benzoyl side chain of the products as well as *ortho*-substitution.

Experimental Section

[Ind_2TiMe_2][8e] and the aminoalkynes **1**–**16**[11] were synthesized according to literature procedures.

Typical Procedure Exemplified by the Reaction of Aminoalkyne 12: (Table 1, entry 12) In an Argon-filled Schlenk tube, a mixture of aminoalkyne **12** (307 mg, 1.00 mmol) and [Ind_2TiMe_2] (15 mg, 0.05 mmol, 5 mol-%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and Pd/C (10% Pd on C, 106 mg, 0.10 mmol Pd, 10 mol-%). After this had been stirred at 25 °C under an atmosphere of O_2 for 24 h, the reaction mixture was filtered through Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 22 g, light petroleum ether/EtOAc, 4:1), compound **28** (266 mg, 0.83 mmol, 83%, R_f = 0.51) was isolated as a yellow solid; m.p. 70 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C): δ = 2.94 (br. t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-CH_2), 4.03 (br. t, $^3J_{H,H}$ = 7.7 Hz, 1 H, CH_2-N), 7.16 (dt, $^3J_{H,H}$ = 8.6, $^4J_{F,H}$ = 1.7 Hz, 2 H, Ar-H), 7.50–7.55 (m, 3 H, Ar-H), 8.10 (dd, $^3J_{H,H}$ = 8.6, $^3J_{F,H}$ = 5.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$, 24 °C): δ = 25.3 (CH_2), 47.1 (CH_2), 115.8 (d, $^2J_{F,C}$ = 22 Hz, CH), 123.5 (q, $^1J_{F,C}$ = 273 Hz, CF_3), 124.2 (q, $^3J_{F,C}$ = 4 Hz, CH), 124.7 (q, $^3J_{F,C}$ = 4 Hz, CH), 126.9 (CH), 129.0 (C), 131.6 (d, $^4J_{F,C}$ = 2 Hz, C), 133.0 (q, $^2J_{F,C}$ = 33 Hz, C), 133.2 (d, $^3J_{F,C}$ = 10 Hz, CH), 138.1 (C), 163.6 (C), 166.3 (d, $^1J_{F,C}$ = 257 Hz, CF), 191.2 (C) ppm. IR (neat): $1/\lambda$ = 2963, 2857, 1671, 1596, 1505, 1318, 1213, 1169, 1144, 1112, 1078, 1060, 1016, 908, 845 cm^{-1}. MS (CI): *m*/*z* (%) = 322 (100) [M + H]$^+$, 293 (4), 123 (7). HRMS: (CI) calcd. ($C_{17}H_{12}F_4NO$) 322.0855; found 322.0860.

Supporting Information (see also the footnote on the first page of this article): Experimental details and complete characterization data of all products, ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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