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1-Tosyl-2-trifluoroacetylindole as Promising Partner for Synthesis of Fused Fluorinated Heterocycles

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Short Communication

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ABSTRACT

We prepared 1-tosyl-2-trifluoroacetylindole - a novel example of an electron-deficient indole with an electrophilic C(3) position. This substance was involved in cyclocondensation with a variety of amidines to propose a new general pathway to 8H-[4,5-b]indolopyrimidines with yield 50-80%. CF_3-containing 5H-[3,2-d]indolopyrimidines were unknown before this study.

Keywords: Electron-deficient indole; amidines; indolopyrimidines; electrophiles; nucleophiles; fluorine.

1. INTRODUCTION

Fused indoles including indolopyrimidines are of significant interest due to the broad spectrum of their biological activity, some of them are target as antitumor drug candidates [1]. CF_3-containing purines [2], are targeted as cytostatic active compound. CF_3-containing indolopyrimidines [3], and their nucleosides [4], are developed as CF_3-purine isosteres. Traditional, synthetic methods of such heterocycles utilize C-3 and C-2 indole reactivity towards electrophiles [5,6].

2. MATERIALS AND METHODS

The *NMR spectrum* was recorded on Bruker ^{TM}300 (300.13 MHz). ^{1}H NMR and ^{13}C NMR

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spectra were taken with TMS as internal standard with operational frequency 300.13 MHz and 75.47MHz respectively. ^{19}F NMR was taken with CF_3CO_2H as an external standard with operational frequency 282.38MHz.

A Finnigan Polaris Q mass spectrometer on direct insertion probe (Dip) with initial temperature 50°C and ionization energy 70Ev was used to record mass spectra. Butyllithium reagent was purchased from either Aldrich or Acros.

1-Tosyl-2-trifluoroacetylindole 1. To a stirred solution of 6 g (22.14 mmol) tosylindole 2 in 120 ml of absolute THF at -60ºC was added 16.6 ml (26.5 mmol, 1.2eq) 1.6 M buthyllithium solution in hexanes. This temperature was maintained for 1.5 h, warmed to -20ºC, and cooled to -60ºC after 20 min. Ethyl trifluoroacetate, 4.7 g (33.21 mmol, 1.5 eq) was added dropwise during 10 min and reaction mixture was left to stand overnight. To the resulted mixture was added 2 ml of water in 10 ml of THF, the solvent removed under reduced pressure, the residue dissolved in ethyl acetate and washed with water. The organic layer dried with $MgSO_4$ and the solvent removed under reduced pressure. Brown oil crystallized spontaneously to yield 7.80 g, (96%), m.p. 79–80°C, ^1H NMR: 2.43(3H, CH_3, s), 7.32-7.34(2H, Ar, d, *J*=8.21Hz), 7.36-7.40(1H, dd, *J1*=7.63Hz, *J2*=7.63Hz), 7.58-7.62(2H, m, Ar, C(3)H), 7.70-7.72(1H, d, *J*=7.92Hz), 7.98-8.00(2H, Ar, d, *J*=8.51Hz), 8.25-8.27(1H, d, J=8.81). ^{13}C NMR 21.63(CH_3), 115.66, 116.27(CF_3, q, *J*=290.74Hz), 122.78(C-(CO)CF_3, q, *J*=2.75Hz), 123.98. 124.77, 127.48, 127.63, 129.72, 129.84, 131.35, 135.47, 140.10, 145.54, 172.74(CO)CF_3, q, *J*=37.8Hz). ^{19}F NMR 5.41(CF_3). Mass spectra, m/z, Intensity: 367(23), M^+; 303(25), M^+-SO_2; 271(24), M^+-$COCF_3$-H; 155(85), $CH_3C_6H_4SO_2^+$; 115(15), M+-$COCF_3$ - $CH_3C_6H_4SO_2$; 91(100), $CH_3C_6H_4^+$;

2-Phenyl-4-trifluoromethyl-(5H)-indolo[3,2-d]pyrimidine 3a. 0.36 g (1 mmol) of compound 1 was dissolved in 5 ml of dioxane followed by addition 0.28 g (1.8 mmol) benzamidine hydrochloride and 0. 25 g (1.8 mmol) potassium carbonate. Resulting suspension was refluxed with stirring for 3hrs, solvent removed by rotary evaporation, triturated with ethyl acetate and distilled water, organic layer separated and dried with $MgSO_4$. Crude product was purified by column chromatography (silica gel, hexanes: ethyl acetate 4:1) to produce 0.25 g (Yield 80%), m.p. 147–148°C.

Anal. Calcd for $C_{17}H_{12}F_3NO_3S$: C 55.58; H 3.29; N 3.81; F 15.52; O 13.07; S 8.73; Found: C 55.43; H 3.33; N 3.41; F 14.95; S 8.13; Mass spectra, m/z, Intensity: 367(100), 298 (56) M^+-CF_3; 278(40) M^+-$CH_3C_6H_4$; 214(32), M^+-$CH_3C_6H_4SO_2$, 69(2) CF_3^+.

Anal. Calcd for $C_{17}H_{10}F_3N_3$: C 65.18; H 3.22; N 13.41; F 18.19. Found: C 65.31; H 3.34; N 12.90; F 17.90. ^1H NMR ($CDCl_3$): 7.10-7.51(9H, m, Ar): 8.64-8.65(2H, d, *J*=8.66Hz), 8.51(1H, s, NH), 8.41-8.42(1H, *J*=7.93Hz), 7.63-7.65(1H, m), 7.54-7.57(2H, meta-Ph, dd, *J1*=7.21Hz, *J2*=7.45Hz), 7.54-7.57(1H, m, Ar), 7.44-7.45(1H, d, *J*=8.41Hz, Ar), 7.36-7.39(1H, dd, para-Ph, *J1*=*J2*=7.45Hz); ^{13}C NMR: 111.98, 120.52, 121.69, 121.98(CF_3, q, *J*=274.22Hz), 122.42, 124.39, 135.79(C-CF_3, q, *J*=37.22Hz), 137.60, 142.31, 151.80, 156.60. ^{19}F NMR: 12.01(CF_3). Mass spectra, m/z, Intensity: 313(100), M^+; 293(5), M^+-HF; 244, M+-CF_3 ; 217(1)M+-CF_3CN-H^+; 190(30), M^+-C_6H_5CN-HF; 167(2), M+-CF_3-C_6H_5; 114(4) $CF_3CH(NH_2)_2$; 102(3), $C_6H_4NC^+$; 91(2), $C_6H_4NH^+$; 77(15) $C_6H_5^+$; 69(2), CF_3^+.

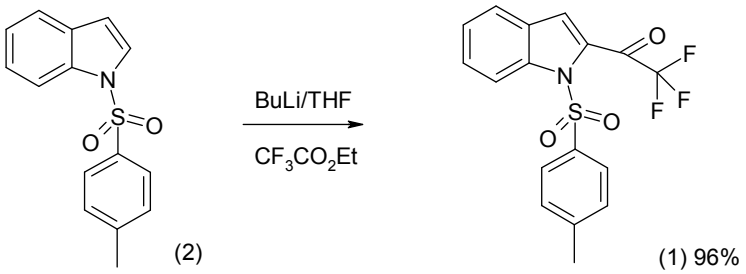
2-Methyl-4-trifluoromethyl-(5H)-indolo[3,2-d]pyrimidine 3b. (Yield 50%) m.p. 164–165°C. Anal. Calcd for $C_{12}H_8F_3N_3$ C 57.38; H 3.21; N 16.73; F 22.69; Found: C 57.13; H 3.09; N 15.90; F 22.07; ^1H NMR: 2.77(3H, s, CH_3), 7.24-7.28(1H, Ar, m), 7.61(1H, Ar, m), 8.14-8.17(1H, d, *J*=7.86Hz), 11.75(1H, s, NH). ^{13}C NMR: 24.99, 95.76, 113.07, 118.73, 121.34, 121.67(CF_3, q, *J*=274.52Hz), 121.83, 123.81, 132.06, 134.77(CF_3, q, *J*=36.49Hz), 143.50, 143.66, 150.94, 157.49. ^{19}F NMR: 13.10(CF_3). Mass spectra, m/z, Intensity: 251(100), M^+; 231(25), M^+-HF; 190(51), M^+-CH_3CN-HF;182(38), M^+-CF_3; 167(7), M+-CF_3-CH_3; 155(10), M^+- CF_3CN-H^+; 141(6), M+-CF_3-CN-CH_3; 114(7) $CF_3CH(NH_2)_2$; 102(5), $C_6H_4NC^+$; 75(9), $C_6H_3^+$; 69(1.5), CF_3^+.

2-Amino-4-trifluoromethyl-(5H)-indolo[3,2-d]pyrimidine 3c. (Yield 70%) m.p. 156–157°C. Anal. Calcd for $C_{11}H_7F_3N_4$: C 52.39; H 2.80; N 22.22; F 22.60; Found: C 52.19; H 2.88; N 21.91; F 22.11. ^1H NMR: 7.12-7.15(1H, d, *J*=7.48Hz), 7.42(2H, s, NH_2), 7.56-7.67(2H, m), 8.08-8.10(1H, d, *J*=7.69Hz), ^{19}F NMR12.63(CF3). Mass spectra, m/z, Intensity: M+: 252(100); 232(56), M+-HF; 213(5), M+-F_2; 205(10), M+-N_2, HF); 190(33), M+-H_2NCN-HF; 183(4), M+-CF_3; 156(26), M+-CF_3CN-H^+; 114(2), $CF_3CH(NH_2)_2$; 102(7), $C_6H_4NC^+$; 91(5), $C_6H_4NH^+$; 75(8), $C_6H_3^+$.

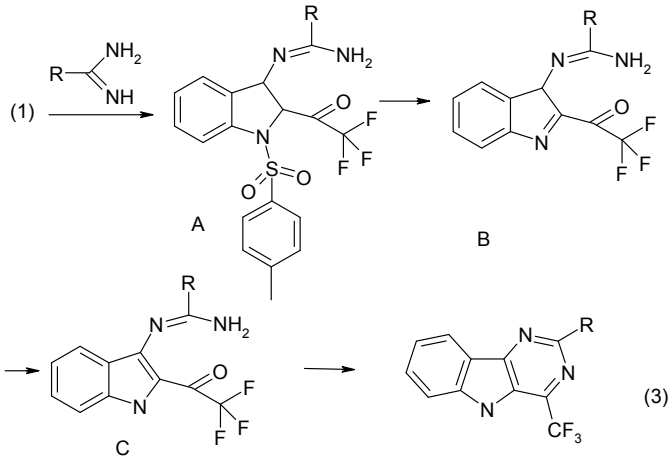
3. RESULTS AND DISCUSSION

In this study we try to develop new synthetic pathway to annelated indole heterocycles by force of imparting of electrophile properties to indole core. Electron-rich indole, typically reactive towards electrophile reagents, possess reactivity to the divergent utility of nucleophiles [7]. This reactivity is especially appealing because these transformation are almost contrary to traditional reactivity of indole. Thus, in recent article, 1,2-bis(phenylsulphonyl)indole was investigated in reactions with C-nucleophiles [8]. In this cases, the presence of N-phenylsulphonyl group was necessary for this reaction resulted in a formal S_N2' or addition-elemination mechanism. 1,2-Bis(phenylsulphonyl)indole undergoes nucleophilic addition with alkylcuprate reagents to give 3-alkyl-2-phenylsulphonyl-(1H)-indoles. The phenylsulfonyl group is a versatile moiety with a powerful electron-withdrawing effect on C(3) position. Elimination of benzenesulfinic acid is essential for indole rearomatisation.

To permit nucleophilic addition to C(3) of indole nucleus, we introduced 1-tosyl functionality and favored (perfluoroalkyl)carbonyl at once. 1-Tosyl-2-trifluoroacetylindole is easily produced from 1-tosylindole through lithiation [9] and a subsequent quench by ethyl trifluoroacetate in high yield (96%) Therein are found explanations for the observed chemical shift differences often observed in trifluoroacetyl groups [10] (Scheme 1).



Through a formal S_N2' or addition-elimination mechanism, 1-tosyl-2-trifluoroacetylindole **1** demonstrated reactivity with a variety of amidines (acetamidine, benzamidine, guanidine) including the first example of amidine addition to indole producing 8H-[4,5-b] pyrimidines **3** with yield 50-80%, R=Ph(a), R=Me(b), R=NH_2(c) (Scheme 2).



In our opinion, initial nucleophilic addition to C(2)-C(3) indole double bond followed by tolylsulfinic acid anion expulsion, result in formation of intermediate B with C(2)-N(1) double bond. Comprising a labile moiety, this bond undergoes 1,3 prototropic rearrangement to restore C(2)-C(3) indole double bond [8], producing C-H substitution product C. Bearing amino and carbonyl functionality in vicinity, intermediate C transforms to pyrimidine in reaction conditions.

4. CONCLUSION

Reactions of 1-tosyl-2-trifluoroacetylindole with amidines have provided the first examples of ambident nucleophiles electrophilically attacking by the indole nucleus with consequent cyclization into 5H-[3,2-d] indolopyrimidines. Though starting indole 1 bear $COCF_3$ substitutent, reaction product obtained from this reaction, comprise the first examples of previously unrecorded CF_3 containing indolo-(5H)-[3,2-d]pyrimidines.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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