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Short Note

3-Methyl 5-{3-[(4-Methylbenzenesulfonyl)oxy]propyl} 4-(2,3-Dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

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Abstract: The 1,4-dihydropyridine is a ubiquitous scaffold employed not only in medicinal chemistry but also in organic synthesis, given its ability to act as a hydrogen transfer reagent, thus emulating NAD(P)H reducing agents. In this work, we describe the synthesis of 3-methyl 5-{3-[(4-methylbenzenesulfonyl)oxy]propyl} 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate as scaffold, which enables downstream derivatization towards new 1,4-dihydropyridine molecules. Inspired by the literature, a new two-step synthesis was planned that involved: (*i*) synthesis of a silylated 1,4-dihydropyridine derivative and (*ii*) deprotection and tosylation in one step using tosyl fluoride.

Keywords: 1,4-dihydropyridine; LTCC; tosylation; building blocks; synthesis

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1. Introduction

The synthesis of 1,4-Dihydropyridines (1,4-DHP) was reported for the first time in 1881 by Arthur R. Hantzsch. It included a multicomponent reaction (MCR) employing two equivalents of ethyl acetoacetate, one equivalent of an aldehyde and a nitrogen source [1]. However, several methods have been developed over the years, including synthetic routes that lead to symmetric, racemic, or enantiopure 1,4-DHPs [2–4].

The 1,4-DHP scaffold is well-known for its prominent role in pharmacologically active compounds and for being used as a model for reducing agents that mimic biological systems. 1,4-DHPs are most commonly known for their use as antihypertensive drugs [5–9] due to their activity as calcium channel blockers. However, the application of the 1,4-DHP core in medicinal chemistry covers a wider range of applications, including anticancer [10] and antimutagenic [11] activities, growth stimulating effect [12], antioxidant properties [12], neuroprotective potential [13], and antimicrobial activity [14]. Throughout the years, the structure-activity relationship (SAR) of 1,4-DHPs has been thoroughly investigated to boost the design of novel structures with increased potency and to modulate the activity toward specific targets [15–19]. The reviews by Ling et al. [20] and Sepehri et al. [21] provide a good overview of the role of 1,4-DHP in drug design.

The 1,4-DHPs exert their pharmacological activity mainly by binding to voltage-gated calcium channels (LTCCs). Given their selectivity toward LTCCs, compounds having a 1,4-DHP core have been employed as tracers in radioligand binding assays and positron emission tomography, mostly bearing ^{3}H and ^{11}C isotopes [22]. Despite the inherent advantages of ^{18}F-labeled tracer candidates, ^{18}F-labeled 1,4-DHPs are rarely described [23], most probably owing to synthetic challenges in accessing these structures. The most straightforward route to radiolabel Csp^3 carbon bonds relies on the use of precursors bearing optimal leaving groups such as tosylates, that would readily undergo S_N2 reactions in the presence of nucleophiles.

Herein, we report the synthesis of 3-methyl 5-{3-[(4-methylbenzenesulfonyl)oxy]propyl} 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**6**), a scaffold

bearing a tosylate leaving group, which enables downstream derivatization to access novel 1,4-DHP derivatives (Figure 1).

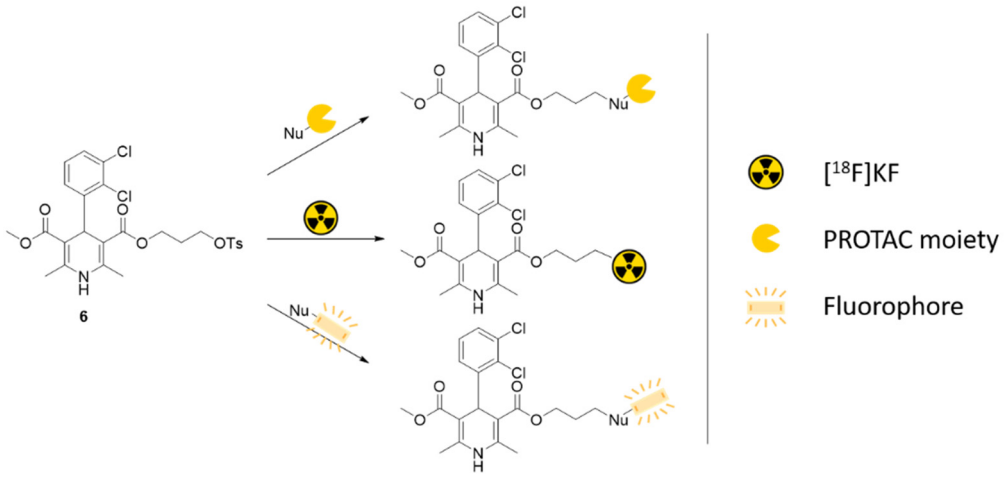
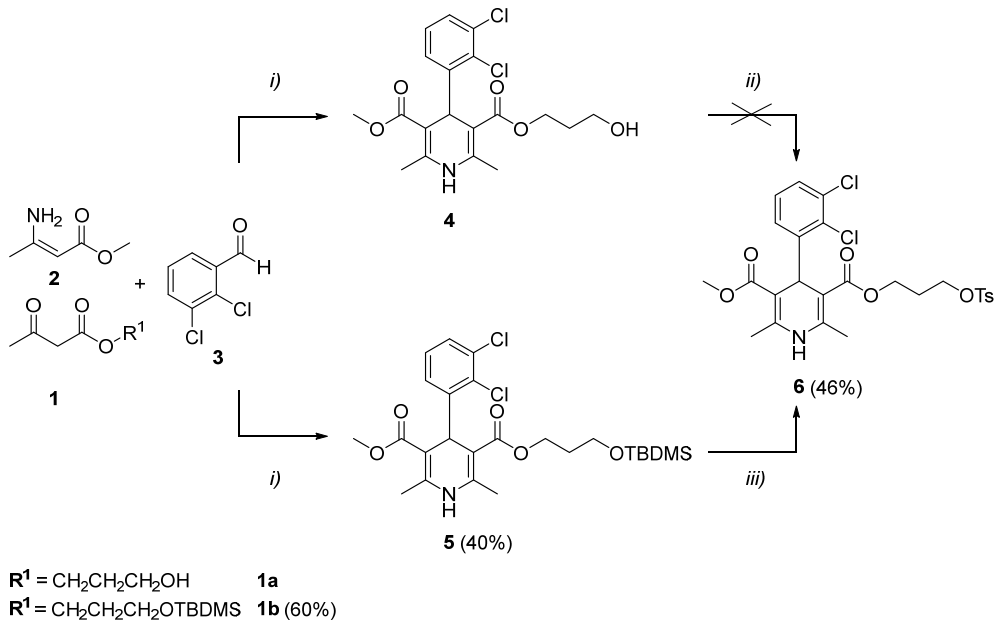


Figure 1. Examples of possible derivatization starting from 6 to access radioligands, PROTACs or fluorescent ligands.

2. Results and Discussion

The proposed synthesis involves two steps, namely, the synthesis of the desired 1,4-DHP scaffold and the tosylation of the propylene linker (Scheme 1). The synthesis of 1,4-DHPs (**4** and **5**) was performed via the Knoevenagel variation of the Hantzsch synthesis, which allows obtaining nonsymmetric 1,4-DHPs in one step.



Scheme 1. The synthetic pathways toward the synthesis of **6** involve the synthesis of the 1,4-DHP scaffold through an MCR and derivatization toward the final product. (*i*) MeOH; (*ii*) Tosyl chloride, Et_3N, DCM; (*iii*) Tosyl fluoride, base, CH_3CN.

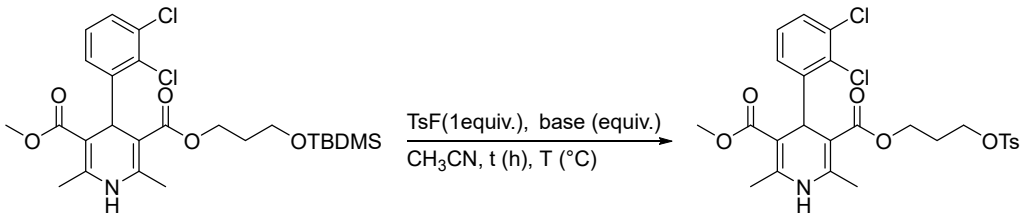
Initially, we planned to access the desired compound **6** via an addition-elimination reaction by reacting the previously synthesized hydroxypropyl derivative (**4**) with tosyl chloride in the presence of a base. Unfortunately, despite the optimization effort, the desired product was never detected. Instead, LC-MS analysis performed on the reaction mixture highlighted the formation of the 3-chloropropyl 1,4-DHP derivative. Chlorinated products

arising from reactions with tosyl chloride are known in the literature [24–26]. Even though primary chloroalkyl adducts are known to undergo S_N2 reactions in the presence of good nucleophiles, the difficulties in separating the chloro derivative from the desired fluoro derivative discourage the use of chlorinated compounds as precursors to access ^{18}F-labeled radiotracers. Therefore, given these limitations, we decided to pursue other synthetic routes to obtain the desired tosylate.

Inspired by literature reports [27], we envisaged that the direct synthesis of the silyl-protected 1,4-DHP **5** could provide an interesting precursor en route to the desired compound **6**. A two-step procedure allowed synthesizing the starting material **1b** from 1,3-propanediol (not shown). Selective monosilylation of 1,3-propanediol in the presence of sodium hydride and TBDMSCl is followed by acetoacetylation of the remaining alcohol function in the presence of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one. This reagent represents a good alternative to the highly lachrymatory and toxic diketene. Furthermore, it does not need acid catalysis and generates only volatile by-products [28]. Then the silylated 1,4-DHP derivative (**5**) was obtained through a Knoevenagel condensation between 2,3-dichlorobenzaldehyde (**3**) and the acetoacetate derivative (**1b**), followed by a Michael addition of **2** to the Knoevenagel product. A final ring closure provides the 1,4-DHP ring. Finally, compound **5** was reacted with tosyl fluoride to yield the desired product **6** in one step.

For the tosylation, catalytic amounts of DBU were initially used at room temperature, following the optimal conditions reported by Gembus et al. [27] (Table 1, entry 1). Compound **6** was formed and isolated, despite the low yield. Thus, a screening of the reaction conditions was performed to improve the yield. First, the reaction temperature was increased, but no product was formed (Table 1, entry 2). Then, DBU was replaced with TBAF (Table 1, entries 3 and 4). The addition of TBAF, being catalytic or stoichiometric, did not benefit the reaction, limiting the formation of **6** to traces detectable only via LC-MS. Since DBU gave still the best results, the number of equivalents used was optimized (Table 1, entries 5 and 6). Sub-stoichiometric amounts of DBU led to a six-fold increase in yield. However, employing stoichiometric amounts of DBU decreased the overall yield.

Table 1. Optimization table.



5 **6**

Entry	Base (Equiv.)	Time (h)	T (°C)	Yield (%)
1	DBU 0.2	24	25	8
2	DBU 0.2	24	70	-
3	TBAF 0.2	48	25	- *
4	TBAF 1	48	25	- *
5	DBU 0.6	24	25	46
6	DBU 1	24	25	30

* The product was detected in traces via LC-MS, but was not isolated.

After the optimization, the conditions reported in entry 6 (Table 1) resulted to be the best in terms of yield, allowing to synthesize **6** in a moderate yield of 46%.

3. Materials and Methods

3.1. General Experimental Information

All chemicals were obtained from commercially available sources and were used without any further purification. All moisture-sensitive reactions were carried out under nitrogen atmosphere in oven-dried glassware. Flash column chromatography was performed using silica (ACROS Silica gel for column chromatography, ultra-pure, 40–60 μM, the average pore diameter of 60 Å), while analytical thin-layer chromatography (TLC) was performed with aluminium-backed EMD Millipore Silica Gel 60 F254 pre-coated plates. Visualization was performed under ultraviolet (UV) light or using appropriate staining solutions. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer (at 400 MHz and 100 MHz, respectively) in chloroform-*d* ($CDCl_3$). The spectra were calibrated using the peak of the deuterated solvent as an internal standard (for $CDCl_3$ 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). HSQC and HMBC spectra were recorded on a Bruker Avance III HD 400 spectrometer. All spectra were measured at room temperature. The δ-values are reported in ppm. Data were acquired and analyzed using Bruker TopSpin 4.0.9 software (Bruker Biospin Corporation, 15 Fortune Drive, Billerica, MA, 01821). LC-MS analyses were recorded on a Thermo Finnigan LCQ Advantage apparatus that includes an Agilent 6110 S Quadrupole MS, Agilent 1100 pump and injection system, and Prevail C18 (3μ) column. The samples were ionized via electron spray ionization (ESI) in the positive mode. For data analysis, ChemStation software rev. B. 04.03-SP2 (Agilent Technologies, Hewlett-Packard-Strasse 8, 76337, Waldbronn, Germany) was used. MS analyses were recorded on a Radian ASAP direct mass detector. IR analyses were recorded on a Bruker Compact Alpha-FTIR Spectrometer.

3.2. Experimental Procedures and Characterization

3-[(tert-butyldimethylsilyl)oxy]propan-1-ol

An oven-dried flask under N_2 atmosphere was charged with NaH 60% p/p (440 mg of suspension equivalent to 264 mg of NaH, 10 mmol, 1 equiv.). Three vacuum-N_2 cycles were applied followed by the addition of anhydrous THF (6 mL) and cooling down to 0 °C. Then 1,3-propanediol (0.76 g, 10 mmol, 1 equiv.) was slowly added and the reaction was left at 0 °C for 30 min. Then a solution of TBDMSCl (1.51 g, 10 mmol, 1 equiv.) in anhydrous THF (6 mL) was added rapidly to the reaction mixture under vigorous stirring. After 30 min, the reaction was quenched with K_2CO_3 and extracted three times with Et_2O. The organic fractions were collected and dried over Na_2SO_4. The solvent was removed under reduced pressure, giving a colorless liquid. The product was used without further purification for the next step [29].

3-[(tert-butyldimethylsilyl)oxy]propyl 3-oxobutanoate (1b)

In a round-bottomed open reaction tube containing xylene (2.5 mL), 3-[(tert-butyldimethylsilyl) oxy]propan-1-ol (1.56 g, 8.20 mmol, 1 equiv.) was added. Then, 2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.17 g, 8.20 mmol, 1 equiv.) was added dropwise to the former solution. The open reaction tube was immersed in an oil bath and heated to 150 °C. After 1 h, the tube was slowly cooled down to room temperature and the reaction mixture was purified via column chromatography (heptane-ethyl acetate 9:1). Evaporation of the solvent under reduced pressure gave 3-[(tert-butyldimethylsilyl)oxy]propyl 3-oxobutanoate as a colorless liquid (1.35 g, 4.92 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 (t, *J* = 6.5 Hz, 2H), 3.6 (t, *J* = 5.9 Hz, 2H), 3.43 (s, 2H), 2.26 (s, 3H), 1.81 (p, *J* = 6.2 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 200.6, 167.3, 62.6, 59.4, 50.2, 31.7, 30.3, 26.0 (3C), 18.4, −5.3 (2C).

3-{3-[(tert-butyldimethylsilyl)oxy]propyl} 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5)

To a round-bottomed flask containing methyl 3-aminocrotonate (**2**, 294 mg, 2.55 mmol, 1 equiv.) a solution of 2,3-dichloro benzaldehyde (**3**, 446 mg, 2.55, 1 equiv.) and **1** (700 mg, 2.55 mmol, 1 equiv.) in methanol (40 mL) was added under vigorous stirring. The reaction mixture was protected from light and heated to reflux in an oil bath. After 24 h, the solvent was evaporated and the crude was purified via column chromatography (heptane-ethyl acetate 7:3) to give **5** as a yellow solid (539 mg, 1.02 mmol, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 7.8 Hz, *J* = 1.6 Hz, 1H), 7.24 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 5.72 (br s, NH), 5.44 (s, 1H), 4.15–4.04 (m, 2H), 3.64–3.45 (m, 5H), 2.30 (s, 3H), 2.29 (s, 3H), 1.80 (p, *J* = 6.3 Hz, 2H), 0.85 (s, 9H), −0.02 (s, 3H), −0.003 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 168.0, 167.5, 148.2, 144.5, 144.3, 133.0, 131.0, 129.7, 128.3, 128.4, 127.2, 103.9, 103.6, 61.3, 59.7, 51.0, 38.7, 31.9, 26.0, 19.8, 19.6, 18.4, −5.3.

3-methyl 5-{3-[(4-methylbenzenesulfonyl)oxy]propyl} 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6)

A round bottom flask containing acetonitrile (1 mL) was loaded with **5** (50 mg, 0.1 mmol, 1 equiv.) and tosyl fluoride (17.4 mg, 0.1 mmol, 1 equiv.), followed by dropwise addition of DBU (8.9 mg, 0.06 mmol, 0.6 equiv.) under vigorous stirring. After 24 h, the reaction mixture was extracted with ethyl acetate. The organic phase was collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude was further purified via column chromatography (heptane-ethylacetate 6:4). The solvent was then evaporated under vacuum to a yellow solid **6** (26.15 mg, 0.05 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.26 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.22 (dd, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 5.98 (br s, NH), 5.32 (s, 1H), 4.02-3.87 (m, 4H), 3.60 (s, 3H), 2.43 (s, 3H), 2.28 (s, 6H), 1.93 (p, *J* = 6.3Hz, 2H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.9, 167.1, 148.2, 145.4, 144.9, 144.3, 133.0, 132.9, 130.7, 130.0, 129.7, 128.5, 128.0, 127.3, 103.7, 103.2, 67.3, 59.8, 51.0, 38.5, 28.4, 21.7, 19.8, 19.5.

MS (ASAP) calculated for $C_{26}H_{26}Cl_2NO_7S^{\cdot+}$ [M$^{\cdot}$+] 567.5; found 567.2.

IR: ν_{max}/cm^{-1} 3336 (NH), 1354 (SO), 1172 (SO).

4. Conclusions

In conclusion, herein we report the synthesis of the tosyl 1,4-DHP derivative **6** in two steps. Given that standard tosylation reaction conditions using tosyl chloride failed to deliver the desired compound, we employed a direct tosylation of the protected silylether using tosylfluoride as a desilylating and tosylating agent. Optimization of the second step allowed isolating **6** as a yellow solid. The final structure of the compound obtained was confirmed by ^{1}H, ^{13}C, HSQC, HMBC, COSY NMR, IR and MS.

Supplementary Materials: NMR and MS analysis: Supporting_info.pdf.

Author Contributions: Conceptualization, E.I.; methodology, C.B., E.I. and S.L.; validation, C.B. and E.I.; formal analysis, C.B. and S.L.; investigation, C.B., E.I. and S.L.; resources, W.M.D.B. and E.I.; data curation, C.B.; writing—original draft preparation, C.B.; writing—review and editing, E.I., W.M.D.B. and C.B.; visualization, C.B. and E.I.; supervision, E.I. and W.M.D.B.; project administration, E.I.; funding acquisition, W.M.D.B. and E.I. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in the Supplementary Materials file or on request from the corresponding author (^{1}H, ^{13}C, 2D-COSY, 2D-HSQC and 2D-HMBC NMR spectra).

Conflicts of Interest: The authors declare no conflict of interest.

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