Synthesis of Tetrasubstituted Thieno[3,2-*b*]pyridin-5(4*H*)-one Derivatives as a Heterocyclic Scaffold for Multisite-specific Fluorous Fluorescent Tagging and Fluorous Solid-Phase Extraction

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Tetrasubstituted thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives were selected as a highly functionalized heterocyclic scaffold for a multisite-specific tagging process utilizing a previously devised fluorous fluorescent tag system. A suitable synthetic method was established for the 7-alkoxy-2,4,6-trisubstituted-thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives, and incorporating *t*-butoxycarbonyl-functionalized building blocks into the reaction sequence produced precursors that could be used in the tagging process. Fluorous solid-phase extraction facilitated the purification of the tagged target compounds after a series of reactions, including *t*-Bu deprotection/*N*-hydroxysuccinimidyl ester formation/amidation.

Keywords: Small molecule microarray, Tag, Fluorous, Fluorescence, Thienopyridinone, Solid-phase extraction

Introduction

Recently, we reported a 7-(1*H*-1,2,3-triazol-4-yl)coumarin-based fluorescent tag system with a fluorous moiety and a polyethylene glycol (PEG) spacer at opposite ends.[1] In that report, we demonstrated its potential utility as a tool for visualizing the individual features of small organic compounds on a fluorous glass slide and for enabling a stepwise, comparative assessment of the fabrication process of small molecule microarrays (SMMs).[2] The preliminary experiment qualitatively analyzed the fluorescence detection results obtained from microarray experiments using tagged biotins as a model for small molecules and streptavidin-Cy3 (and avidin-Cy5) as the binding partners. Our next intention was to construct a model SMM consisting of small organic compounds with and without previously known protein partners. The purpose was to prove that our format is favorable for the practical fabrication of SMMs and the detection of binding phenomena between small organic compounds and proteins of interest. Initially, we concentrated on the selection of a heterocyclic scaffold that could be appropriately elaborated. This would eventually form the framework for heterocyclic compound library candidates comprising a proportion of the model SMMs, and it would also be used in trial experiments for the establishment of an effective tagging process using the fluorous fluorescent tag system.

With respect to small molecule immobilization strategies for SMM fabrication,[2] there have been several efforts to develop covalent and site-non-specific immobilization methods[3] for diversifying the possible binding orientations of covalently[3a–c]/noncovalently[3d] immobilized small organic molecules, to overcome the disadvantage of "monosite-specific" immobilization strategies. These approaches utilized a photo-cross-linking process between covalently[3a,b]/noncovalently[3d] 3-aryl-3-trifluoromethyldiazirine-modified surfaces or a covalently diazoketone-modified surface[3c] and small organic molecules. As schematically represented in Figure 1, we envisioned that a "multisite-specific" tagging process for appropriately designed heterocyclic compound libraries using the fluorous fluorescent tag system, followed by a spotting process for immobilization of the tagged compounds, could serve as an alternative approach for increasing the molecular diversity of compound libraries on glass slides and possibly improving the probability of finding their binding protein partners. Furthermore, the tagging process could be facilitated by fluorous solid-phase extraction (F-SPE)[4] because of the presence of a fluorous moiety in the tag system. The overall process would result in the noncovalent and multisite-specific immobilization of the compound libraries. To the best of our knowledge, this process has not been reported in the field of SMMs.

In this context, herein, we would like to report the synthesis of tetrasubstituted thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives and a preliminary example of their multisite-specific tagging capability. As exemplified in Figure 2, together with the values of some physicochemical parameters,[5] the thieno[3,2-*b*]pyridin-5(4*H*)-one ring system (**1**) has played a role in the isosteric replacements of biologically active quinolin-2(1*H*)-one derivatives (**2**) during explorations of their structure-activity/property relationships, and it seemed that there would be room for a stand-alone investigation of the

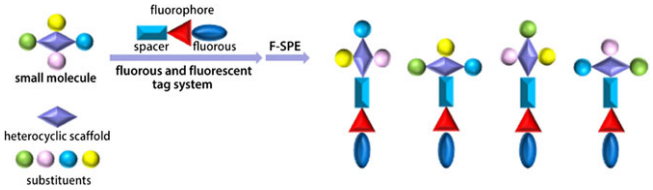


Figure 1. Multisite-specific tagging process.

template as a starting point for novel biological activities through substitutions around the system.[6,7] We chose to pursue 7-alkoxy-2,4,6-tri-substituted-thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives (**3**, Figure 3) as an example of tetrasubstituted thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives because we believed that the structures were suitable to our aims. Moreover, they were structurally novel and synthetically readily accessible. The synthetic method is based on the sequential introduction of substituents onto the ring system by the Suzuki coupling reactions of 3-amino-5-bromothiophene-2-carboxylate, trifluoroacetyl-activated Mitsunobu reactions, acetylation reactions, and Dieckmann-like condensation/alkylation reactions to afford 7-alkoxy-2,4,6-trisubstituted-thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives. The selection of appropriately functionalized building blocks in each substituent-introducing step would enable the resulting derivatives to enter the tagging process using the fluorous fluorescent tag system.

Experimental

Experimental and characterization details may be found in the Supporting Information.

Results and Discussion

The thieno[3,2-*b*]pyridin-5(4*H*)-one compound **3a** was selected as a prototypical example of a 7-alkoxy-2,4,6-tri-substituted-thieno[3,2-*b*]pyridin-5(4*H*)-one derivative and was synthesized as shown in Scheme 1. Methyl 3-amino-5-bromothiophene-2-carboxylate (**4**) was obtained through a previously reported reaction sequence[8] from methyl 3-aminothiophene-2-carboxylate.[9] The bromide (**4**) was subjected to a Suzuki coupling reaction with (4-fluorophenyl)boronic acid (**5a**), under typical conditions, to give 3-amino-5-(4-fluorophenyl)thiophene-2-carboxylate (**6a**) in 95% yield.[10,11] The *N*-trifluoroacetylated derivative **7a**, obtained at room temperature in 98% yield by the treatment of compound **6a** with trifluoroacetic anhydride in the presence of pyridine in DCM, underwent a Mitsunobu reaction[12] with benzyl alcohol (**8a**) under DIAD/PPh_3/THF conditions at room temperature to give the *N*-benzylated derivative (**9a**) in 88% yield.[13] After its de-trifluoroacetylation with K_2CO_3 in THF/MeOH/H_2O at room temperature (98% yield), 3-benzylamino-5-(4-fluorophenyl)thiophene-2-carboxylate (**10a**) was acetylated with 3-(4-methoxyphenyl)propanoic acid (**11a**) in the presence of $POCl_3$ and pyridine in DCM at room temperature[14] to give the *N*-[3-(4-methoxyphenyl)] propanoyl derivative (**12a**) in 64% yield. The final Dieckmann-like condensation/alkylation step was accomplished in one pot by the treatment of compound **12a** with KHMDS in THF at −78°C followed by the addition of methyl mesylate and elevation of the reaction temperature to room temperature to afford the target compound **3a** in 77% yield. In the trifluoroacetyl-activated Mitsunobu

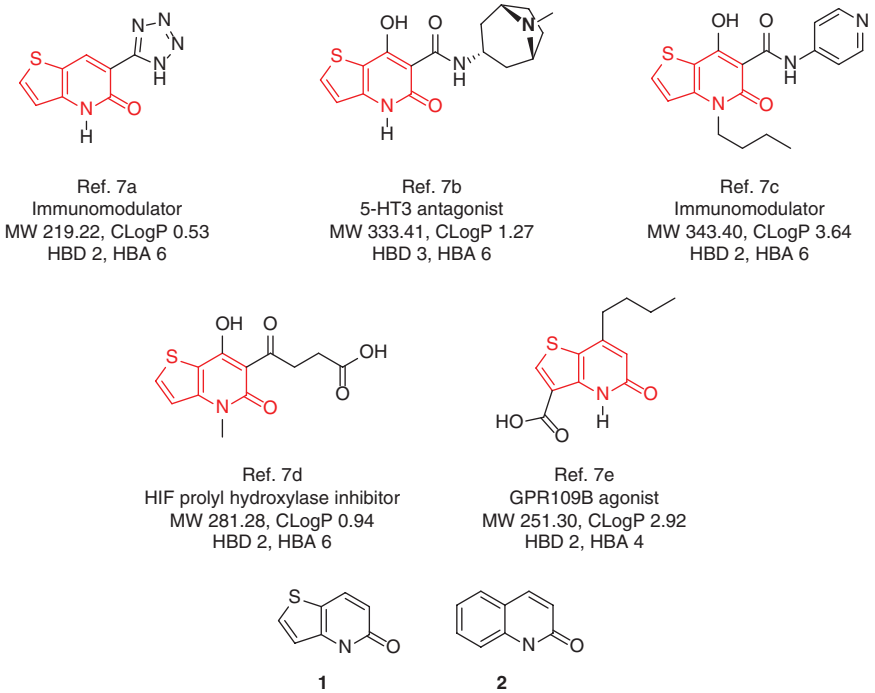


Figure 2. Representative of biologically active thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives.

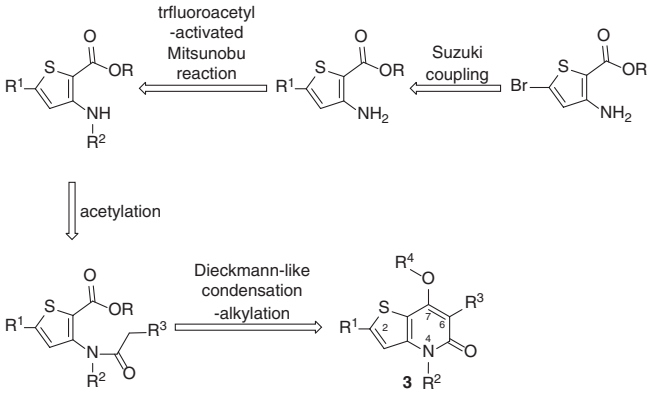
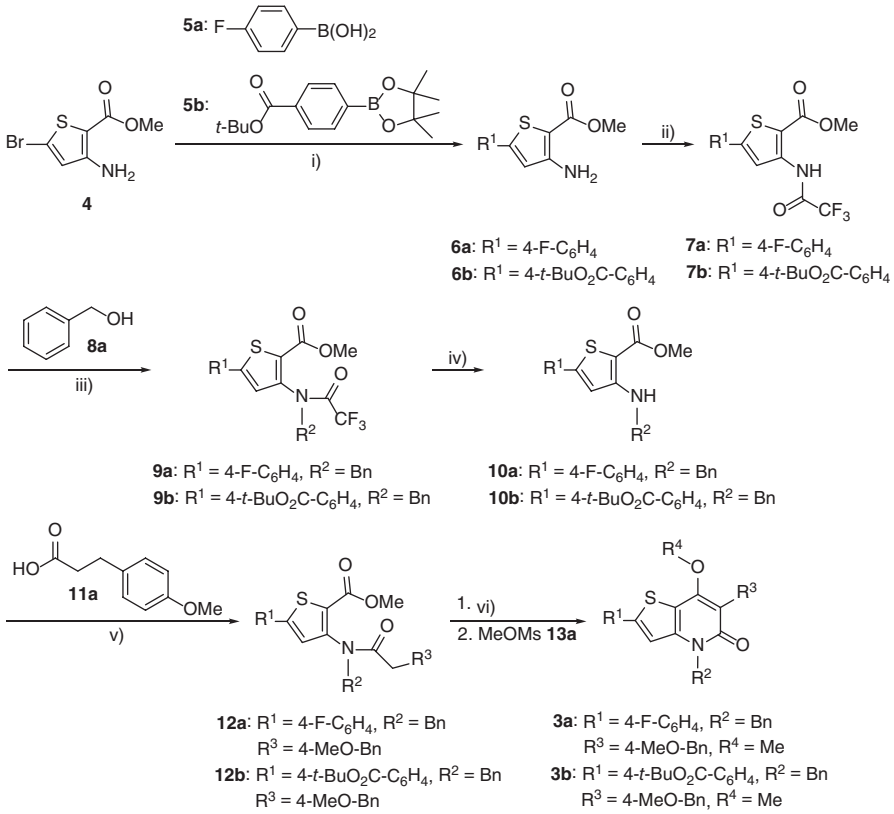


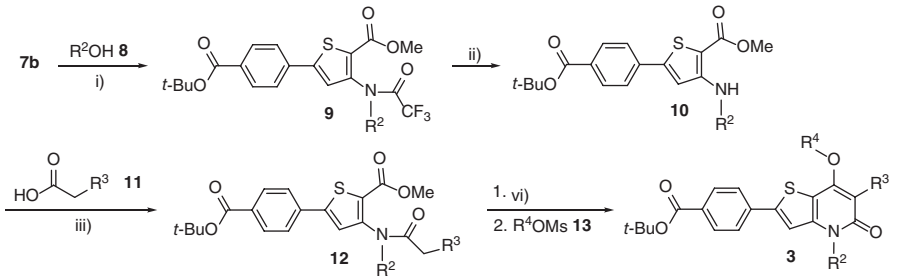
Figure 3. Synthetic strategy for 7-alkoxy-2,4,6-tri-substitued-thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives.

reaction and Dieckmann-like condensation/alkylation step, neither significant *O*-benzylation nor *C*-methylation was observed. Subsequent to the establishment of the synthetic method for 7-alkoxy-2,4,6-tri-substitued-thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives, the corresponding derivative **3b**, with a 4-(*t*-butoxycarbonyl)phenyl group in place of the 4-fluorophenyl group at the 2-position was synthesized. This sequence began with the Suzuki coupling of bromide **4** and *t*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoate (**5b**)[9,15] and subsequently followed the reaction steps depicted in Scheme 1. Compound **3b** would be utilized for the site-specific tagging of the ring system using the fluorous fluorescent tag system (*vide infra*). Notably, the use of NaO^{t}Bu, KO^{t}Bu, NaH, LHMDS, or LDA, instead of KHMDS, in the Dieckmann-like condensation step for compound **12b** had deleterious effects on product formation. Except for compound **6a**,[16] every compound (*viz*. **6b**, **7a**, **7b**, **9a**, **9b**, **10a**, **10b**, **12a**, **12b**, **3a and 3b**) was unknown and therefore was characterized on the basis of ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

Before proceeding with the introduction of suitable building blocks at positions other than the 2-position of the ring system for the tagging process, we examined the installation of different substituents at the 4, 6, and 7 positions of the thieno[3,2-*b*]pyridin-5(4*H*)-one skeleton. Starting from compound **7b**, we incorporated alcohols (**8**), mono-substituted acetic acids (**11**), and alkyl mesylates (**13**)[9] as building blocks (Scheme 2); the results are summarized in Table 1. The trifluoroacetyl-activated Mitsunobu reactions of compound **7b** with isobutyl alcohol (**8b**), 4-fluorobenzyl alcohol (**8c**), and thiophen-2-ylmethyl alcohol (**8d**) gave the desired *N*-alkylated products **9c–e**, respectively, as major products.[17] The *N*-alkylated products **9 c–e** were de-trifluoroacetylated and subsequently acetylated



Scheme 1. (i) $PdCl_2(PPh_3)_2$, Na_2CO_3, 1,4-dioxane/H_2O, 90°C, 95% for **6a**, and $Pd(OAc)_2$, PPh_3, Na_2CO_3, 1,4-dioxane/H_2O, 95°C, 94% for **6b**; (ii) trifluoroacetic anhydride, pyridine, DCM, rt, 98 and 100% for **7a** and **7b**; (iii) DIAD, PPh_3, THF, rt, 88 and 91% for **9a** and **9b**; (iv) K_2CO_3, THF/MeOH/H_2O, rt, 98 and 100% for **10a** and **10b**; (v) $POCl_3$, pyridine, DCM, rt, 64 and 63% for **12a** and **12b**; (vi) KHMDS, THF, −78°C to rt, 77 and 74% for **3a** and **3b**.



Scheme 2. (i) DIAD, PPh_3, THF, rt; (ii) K_2CO_3, THF/MeOH/H_2O, rt; (iii) $POCl_3$, pyridine, DCM, rt; (iv) KHMDS, THF, −78°C to rt.

Table 1. Yields of compounds **9c–e**, **10c–e**, **12c–h**, and **3c–l**.

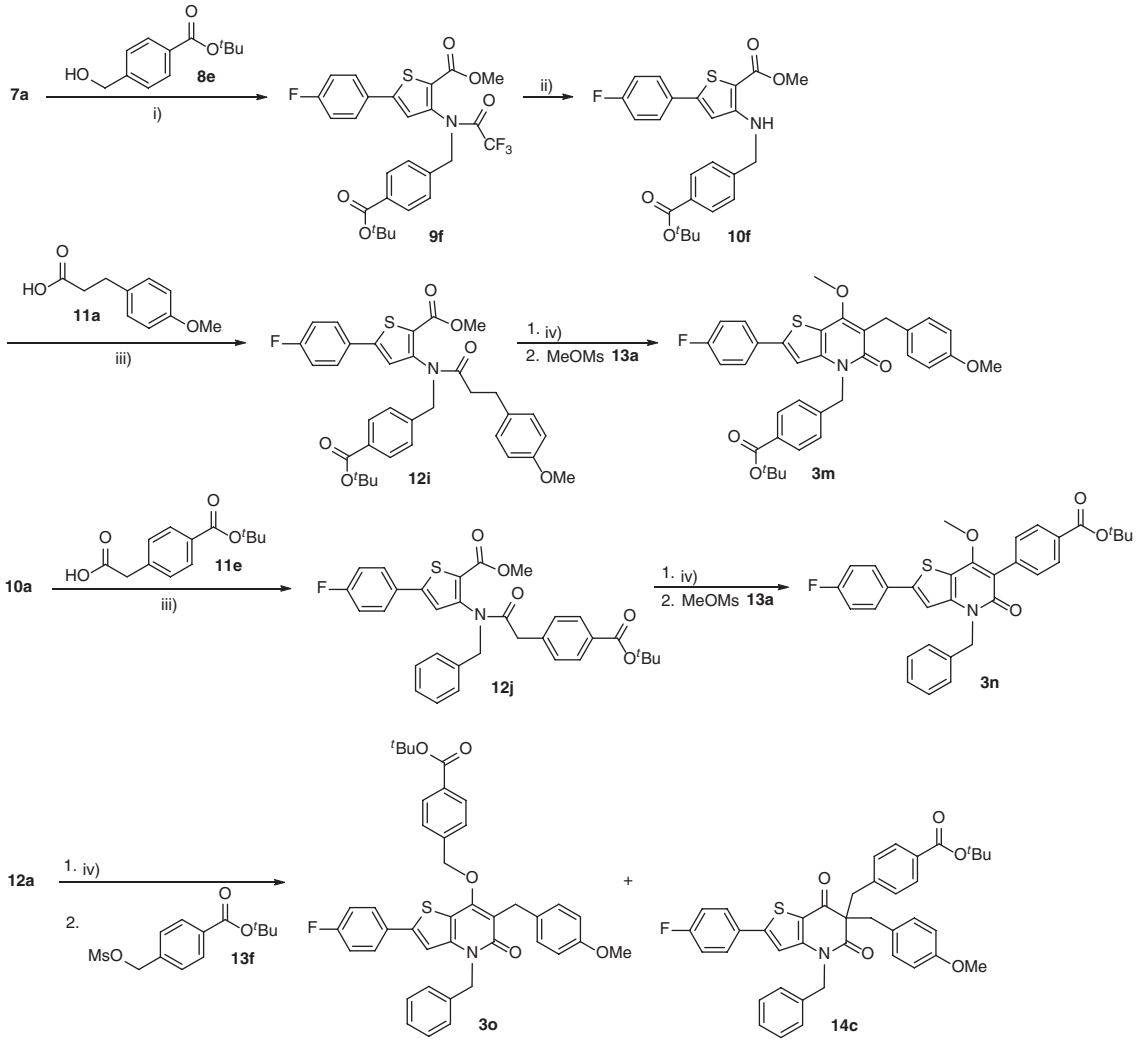
Compd	R^2	R^3	R^4	Yield (%)
9c	*i*-Bu	-	-	64
9d	4-F-Bn	-	-	87
9e	Thiophen-2-ylmethyl	-	-	50
10c	*i*-Bu	-	-	99
10d	4-F-Bn	-	-	94
10e	Thiophen-2-ylmethyl	-	-	98
12c	*i*-Bu	4-MeO-Bn	-	62
12d	4-F-Bn	4-MeO-Bn	-	74
12e	Thiophen-2-ylmethyl	4-MeO-Bn	-	66
12f	Bn	3-MeO-Bn	-	74
12g	Bn	PhO	-	97
12h	Bn	4-MeO-phenethyl	-	79
3c	*i*-Bu	4-MeO-Bn	Me	61
3d	4-F-Bn	4-MeO-Bn	Me	63
3e	Thiophen-2-ylmethyl	4-MeO-Bn	Me	50
3f	Bn	3-MeO-Bn	Me	69
3g	Bn	PhO	Me	67
3h	Bn	4-MeO-phenethyl	Me	67
3i	Bn	4-MeO-Bn	Et	-[a]
3j	Bn	4-MeO-Bn	*i*-Pr	-[a]
3k	Bn	4-MeO-Bn	Allyl	38(8)[b]
3l	Bn	4-MeO-Bn	Propargyl	28(23)[b]

[a] The corresponding product was not obtained.
[b] The number in parenthesis is the yield for the corresponding *C*-alkylated 4,5,6,7-tetrahydrothieno[3,2-*b*]pyridine-5,7-dione derivatives **14a** and **14b**.

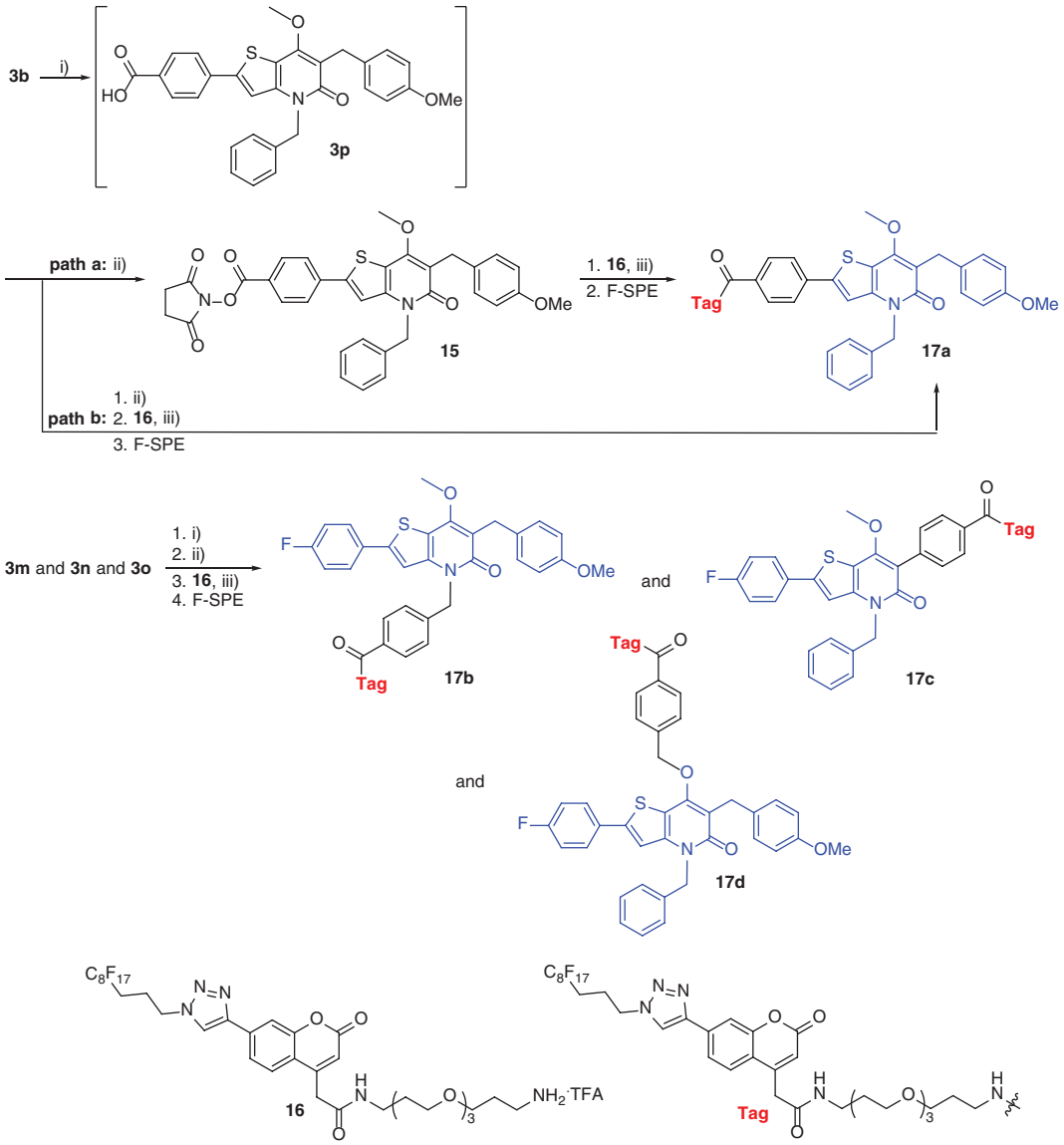
with 3-(4-methoxyphenyl)propanoic acid (**11a**) to afford 3-alkylamino-5-[4-(*t*-butoxycarbonyl)phenyl]thiophene-2-carboxylates (**10c–e**) and their *N*-[3-(4-methoxyphenyl)] propanoyl derivatives (**12c–e**) in excellent and fair yields, respectively. Compound **10b** (Scheme 1) was acetylated with 3-(3-methoxyphenyl)propanoic acid (**11b**), 2-phenoxyacetic acid (**11c**), and 4-(4-methoxyphenyl)butanoic acid (**11d**) to give the acetylated derivatives **12f–h** in good to excellent yields. The precursors **12c–h** yielded thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives **3c–h** in fair yields when subjected to one-pot Dieckmann-like condensation/methylation conditions. Meanwhile, compound **12b** (Scheme 1), on treatment with KHMDS at −78°C in THF followed by the addition of allyl mesylate (**13d**) and propargyl mesylate (**13e**) and elevation of the reaction temperature to room temperature, yielded the *O*-alkylated target compounds **3k and 3l** in 38 and 28% yields, respectively, along with the formation of the corresponding *C*-alkylated products in 8 and 23% yields. In the case of ethyl mesylate (**13b**) and isopropyl mesylate (**13c**), the corresponding target products were not obtained,[18] and further work on the optimization of the reaction conditions was not performed. Previously unknown compounds **9c–e**, **10c–e**, **12c–h**, **3c–h**, and **3k and 3l** were characterized on the basis of ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data. Moreover, the 4,5,6,7-tetrahydrothieno[3,2-*b*] pyridine-5,7-dione derivatives **14a**, **14b**, which correspond to compounds **3k and 3l**, were also unknown and were characterized on the basis of ^{1}H NMR, MS, and HRMS spectral data.

We next turned our attention to the installation of functionalized units that would be suitable for reaction with the fluorous fluorescent tag system. Thus, building blocks with the *t*-butoxycarbonyl group, such as the alcohol **8e**,[9,19] acetic acid **11e**,[9,20] and mesylate **13f**,[9] were prepared based on methods described in the literature and incorporated according to Scheme 1 by reactions with the 4-fluorophenyl derivatives **7a**, **10a**, and **12a**, respectively, as shown in Scheme 3. The reaction sequence finally afforded thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives **3m–o**, which would be used in the multisite-specific tagging process. Notably, the treatment of compound **12a** with the mesylate **13f** yielded a 4,5,6,7-tetrahydrothieno[3,2-*b*]pyridine-5,7-dione derivative **14c** as the major product; further work on the optimization of the reaction conditions was not performed because the obtained amount of target compound **3n** was sufficient for use in the next step. Compounds **9f**, **10f**, **12i**, **10j**, **3m–o**, and **14c** were all unknown and were fully characterized on the basis of ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

As presented in Scheme 4, compound **3b** was deprotected by treatment with TFA at room temperature to afford the carboxylic acid intermediate **3p**. Compound **3p** was transformed into the *N*-hydroxysuccinimidyl (NHS) ester **15** under typical conditions in 97% purified yield (Scheme 4, path a). When ester **15** was treated with a 0.9 molar equivalent of TFA salt **16** of the fluorous fluorescent tag system[1,9] in the presence of TEA in DMF at room temperature, compound **17a** was obtained in 78% yield and was spectroscopically pure by ^{1}H NMR after F-SPE.[4,9] Completion of the reaction and elution of the target compound **17a** during the F-SPE was monitored by fluorescence detection on a silica gel thin-layer chromatography (TLC) plate for the reaction mixture and the fractions obtained from the extraction. The used fluorous silica gel column was recovered by washing with MeOH several times and reused. The multistep procedures were operationally simplified by using the crude NHS ester obtained by the evaporation of the filtrate of the reaction mixture in the ester-forming step. A sequence of (1) *t*-Bu



Scheme 3. (i) DIAD, PPh_3, THF, rt, 92% for **9f**; (ii) K_2CO_3, THF/MeOH/H_2O, rt, 98% for **10f**; (iii) $POCl_3$, pyridine, DCM, rt, 75 and 73% for **12i** and **12j**; (iv) KHMDS, THF, −78°C to rt, 65, 72, and 21% (with 79% of **14c**) for **3m**, **3n**, and **3o**.



Scheme 4. (i) TFA, rt, 99% for **3p**; (ii) NHS, DCC, THF, rt, 99% for **15**; (iii) TEA, DMF, rt, 78% (path a)/76% (path b), 59, 86, and 50% for **17a**, **17b**, **17c**, and **17d**.

deprotection reaction/evaporation; (2) NHS ester formation reaction/filtration/evaporation; (3) amide formation reaction/evaporation; and (4) F-SPE/evaporation, as presented for compound **3b** in Scheme 4 (path b), afforded the ^{1}H NMR spectroscopically pure form of the final compound **17a** in 76% overall yield for the three steps. The protocol was also successfully applied to the tagging of precursors **3m–o**, resulting in the formation of **17b–d** connected with the tag system at the 4, 6, and 7 positions of the ring system in high three-step overall yields (Scheme 4). Novel compounds **15** and **17a–d** were characterized on the basis of ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data. Compound **3p** was characterized on the basis of ^{1}H NMR, MS, and HRMS spectral data. The above results suggest that the tagging process could be adapted in a high-throughput parallel fashion.

Conclusion

We selected tetrasubstituted thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives as a highly substituted heterocyclic scaffold for a multisite-specific tagging process utilizing a previously devised fluorous fluorescent tag system. A synthetic method was first established for the 7-alkoxy-2,4,6-tri-substituted-thieno[3,2-*b*]pyridin-5(4*H*)-one derivatives. Incorporating *t*-butoxycarbonyl-functionalized building blocks into the reaction sequence yielded precursors that could enter the tagging process. Fluorous solid-phase extraction facilitated the purification of the tagged target compounds from a series of reactions consisting of *t*-Bu deprotection/NHS ester formation/amide formation, thus suggesting its adaptability in a high-throughput parallel manner. As mentioned in the introduction, our next research objective will be to prepare a

model SMM consisting of small organic molecules with and without previously known protein partners, including the tagged compounds described in this report.

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