Facile Synthesis of 4-Arylsulfanylcoumarin Library through Reaction of 4-Tosyloxycoumarins with Thiols on Solid Phase

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Diversified 4-arylsulfanylcoumarins were generated under extremely mild conditions on solid phase with a silyl linker based macro-beads by base-promoted reaction of 4-tosyloxycoumarins with thiols.

The introduction of sulfur as a heteroatom in many molecules was shown to be an effective method for imparting significant biological activity.[1] Coumarin, an important class of drug-like molecule with unique pharmaceutical and biological properties, has generated a considerable interest both in academia and industry. As a result, there have been numerous efforts to develop efficient methodologies for its synthesis.[2] In light of our interest in coumarin chemistry,[3] we required an efficient method to generate a 4-sulfide based coumarin library with a hope to find some interesting lead compounds for our particular biological assays. In this paper, we report a superior method for the synthesis of diversified 4-arylsulfanylcoumarins from the corresponding 4-tosyloxycoumarins and thiols under extremely mild conditions with excellent yields, which ultimately led to a 4-arylsulfanylcoumarin library on a silyl linker based macrobeads.

Although 4-arylsulfanylcoumarins have been synthesized repeatedly either for biological evaluation or as key intermediates in synthesizing complex molecules, their syntheses suffer from multiple synthetic steps, harsh reaction conditions (such as the use of stoichiometric amounts of bases, or toxic reagents often under high temperatures), and poor substituent tolerance.[4] Since we are interested in synthesizing libraries on a silyl linker based high-capacity polystyrene macro-beads[5] as an indispensable requirement to realize a key element in a one-bead, one-compound per well technology platform,[5b] we could not utilize the conditions illustrated above. This is due to the incompatibility between the extreme conditions used for the functionalization of the coumarin scaffold and the selected solid support. Therefore, we had to search for alternative mild reaction conditions that not only are compatible with substrates and the solid support, but could also proceed at room temperature as a requirement to prevent fracturing of the polystyrene based macrobeads, which normally occurs at an elevated temperature.

Recently, we identified 4-tosyloxycoumarin as an ideal electrophile in palladium-catalyzed cross-coupling reactions to generate 4-substituted coumarins.[3] We assumed that this substrate may also under 1,4-addition, followed by elimination when reacted with nucleophiles since the structure of this enol tosylate is in α,β-conjugated system.

Similar nucleophilic vinylic substitutions of this kind of structure were observed previously.[6] To test this idea, 4-tosyloxycoumarin (**1a**) was prepared and reacted with benzenethiol in the presence of triethylamine in CH_2Cl_2. To our delight, this reaction was finished in less than 2 min at room temperature in almost quantitative yields. It is also noteworthy that this reaction

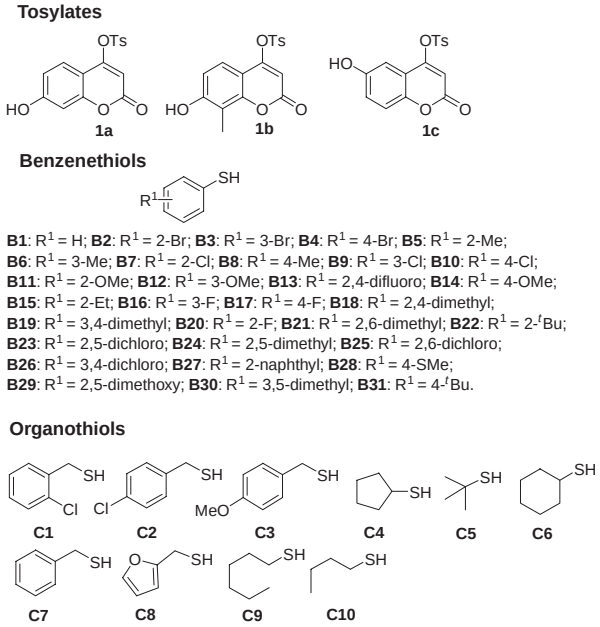
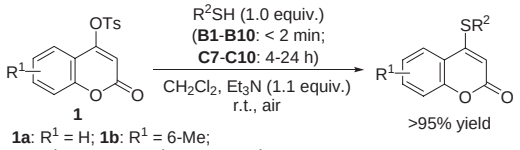


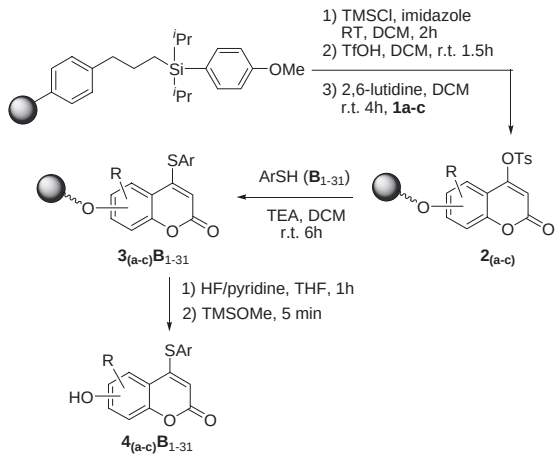
Figure 1.

could be carried out at room temperature under air atmosphere. To demonstrate the generality of this method, we next investigated the scope of this reaction (Scheme 1). This reaction was highly efficient. When substituted benzenethiol **B1**–**B10** (Figure 1) were used, all reactions were completed *in two minutes* to give the corresponding products in almost quantitative yields. While, when organomercaptans **C7–C10** were employed, the reaction time was extended to 4–24 h, and usually a yield of desired products higher than 95% was obtained in all the cases.

The exceptional efficiency for this base accelerated reaction led us to apply this methodology on solid-phase synthesis of 4-arylsulfanylcoumarin library. In order to link the tosylates substrates to the silyl linker based macrobeads (500–600 μm, generated based on the method described by Schreiber[5a] from unfunctionalized polystyrene, which was purchased from Rapp Polymere GmbH), the substrates (**1a**–**1c**) (Figure 1) were synthesized[7] and then loaded on the solid support (loading: 100–120 nmol).[5] (Scheme 2) These on beads tosylates were first reacted in parallel with 31 benzenethiols ($\mathbf{B}_{1-31}$, 5 equiv.) and



Scheme 1.



Scheme 2. Library synthesis on solid phase.

Table 1. Solid-phase library synthesis[a]

Product	Purity	Product	Purity	Product	Purity
4a-B1	94.1%	**4b-B1**	>99%	**4c-B1**	98.4%
4a-B2	94.6%	**4b-B2**	98.9%	**4c-B2**	>99%
4a-B3	91.8%	**4b-B3**	>99%	**4c-B3**	95.3%
4a-B4	>99%	**4b-B4**	>99%	**4c-B4**	98.9%
4a-B5	89.2%	**4b-B5**	96.9%	**4c-B5**	>99%
4a-B6	83.6%	**4b-B6**	97.6%	**4c-B6**	97.8%
4a-B7	96.5%	**4b-B7**	>99%	**4c-B7**	>99%
4a-B8	90.9%	**4b-B8**	>99%	**4c-B8**	95.7%
4a-B9	93.1%	**4b-B9**	>99%	**4c-B9**	96.3%
4a-B10	97.7%	**4b-B10**	>99%	**4c-B10**	97.4%
4a-B11	>99%	**4b-B11**	93.6%	**4c-B11**	>99%
4a-B12	>99%	**4b-B12**	98.5%	**4c-B12**	>99%
4a-B13	>99%	**4b-B13**	94.8%	**4c-B13**	>99%
4a-B14	94.3%	**4b-B14**	>99%	**4c-B14**	>99%
4a-B15	95.4%	**4b-B15**	>99%	**4c-B15**	97.7%
4a-B16	>99%	**4b-B16**	96.4%	**4c-B16**	>99%
4a-B17	>99%	**4b-B17**	98.3%	**4c-B17**	>99%
4a-B18	85.9%	**4b-B18**	>99%	**4c-B18**	91.6%
4a-B19	77.8%	**4b-B19**	92.3%	**4c-B19**	90.0%
4a-B20	97.9%	**4b-B20**	95.5%	**4c-B20**	>99%
4a-B21	87.0%	**4b-B21**	92.2%	**4c-B21**	96.4%
4a-B22	88.0%	**4b-B22**	72.9%	**4c-B22**	93.6%
4a-B23	94.2%	**4b-B23**	>99%	**4c-B23**	>99%
4a-B24	94.5%	**4b-B24**	97.7%	**4c-B24**	98.0%
4a-B25	97.7%	**4b-B25**	>99%	**4c-B25**	>99%
4a-B26	93.8%	**4b-B26**	98.0%	**4c-B26**	97.0%
4a-B27	98.2%	**4b-B27**	>99%	**4c-B27**	98.2%
4a-B28	94.1%	**4b-B28**	>99%	**4c-B28**	97.0%
4a-B29	95.3%	**4b-B29**	97.7%	**4c-B29**	>99%
4a-B30	83.5%	**4b-B30**	94.3%	**4c-B30**	94.9%
4a-B31	74.9%	**4b-B31**	84.5%	**4c-B31**	85.0%

[a]Purities were determined by LC-MS.

10 organothiols ($\mathbf{C}_{1-10}$, 5 equiv.), respectively, (Figure 1) and then cleaved from the beads. The results are summarized below (Table 1). It is interesting to notice that all the benzenethiols-based reactions gave the corresponding products in high yields (more than 90%) as was confirmed with LC-MS, and the reactions only needed 6 h at room temperature under air atmosphere for completion. On the other hand, the organothiols-based reactions proceeded extremely slowly and no significant conversions were observed when the reactions proceeded at room temperature for 4 days. This library was synthesized only in two days. The operation is very simple and the compounds were released by treating with HF·pyridine and TMSOMe subsequently. The purity of this library was analyzed by LCMS and the results were almost perfect. Most of them were over 90% pure which could be directly used for biological assay. Further investigation for this category of substrates is underway in our lab.

In conclusion, we have developed a highly efficient and convenient approach for the synthesis of diversified 4-arylsulfanyl-coumarins library under extremely mild reaction conditions. This method should allow us to construct a larger 4-arylsulfanyl-coumarins library fast and effectively. The screening for biological activity of these small molecules is under investigation in our laboratory.

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