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Synthesis and properties of a new SASRIN resin derivative: SASRIN–2-pyridylthiocarbonate (SASRIN–TOPCAT) resin

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Abstract

A new SASRIN resin derivative, SASRIN–TOPCAT resin, was synthesized by the reaction of SASRIN resin with 2-thiopyridyl chloroformate. The new resin can be used for the loading of alcohols and thiols under neutral conditions, and the release of alcohol from the resin is achieved by the treatment of 1% TFA in CH_2Cl_2 for 15–60 min. Compared to the other reported resins, SASRIN–TOPCAT resin is more suitable for the loading of alcohols in solid-phase organic synthesis.

Keywords: SASRIN resin derivative; Etherification; Solid-phase organic synthesis

Resins bearing alcohols are widely used as building blocks in solid-phase organic synthesis (SPOS). The success of solid-phase reactions with resin bearing alcohols has generated a tremendous interest in expanding the applications of combinatorial synthesis.[1] In general, the construction of an ether linkage of alcohols to the solid support is more synthetically challenged. Etherification usually requires harsh reagents and conditions, such as strong bases and acids. However, for the synthesis of compounds containing multi-functional or acid-sensitive groups by SPOS, immobilization of alcohol substrates on the solid support should be reacted under neutral conditions, and the cleavage of the ether linkage for the release of products from resin is preferred by using mild acidic reagents. Many types of resin, such as Wang resin[2] and dihydropyranyl (DHP) resin,[3] have been used for the alcohol loading under mild conditions based on their acid-sensitive ether linker. Hanessian introduced Wang-trichloroacetimidate resin[4] and Wang-2-pyridylthiocarbonate (Wang-TOPCAT) resin[5] for the preparation of the resin bearing alcohols under weak acidic and neutral conditions, respectively. They also described that alcohols could be released from Wang resin with 1–10% TFA in CH_2Cl_2. However, the reports from the same group and other research groups[6] noted that the cleavage of ether linker on Wang resin was always performed under 10–95% TFA in CH_2Cl_2. 2-Cl–Trityl resin is another acid-sensitive resin derivative, which has been used widely for loading the alcohol under mild conditions, and the cleavage of the ether linkage is completed with 1% TFA in CH_2Cl_2.[7] However, 2-Cl–trityl resin is very temperature- and moisture-sensitive and usually stored in a refrigerator before use, which leads to the variable results in its application. In addition, 2-Cl–trityl resin contains a bulky group and can only be used to anchor the primary hydroxyl group. It was reported that Fmoc-threoninol(*t*Bu) reacted with 2-Cl–trityl resin, giving an initial loading of 1.39 mmol/g with the production of a substitution level of 0.15 mmol/g after 22 h and only in a yield of 14.6%.[8]

SASRIN® (Super Acid Sensitive Resin) resin is a very acid-sensitive resin and was first developed by Merger et al.[9] SASRIN resin and its derivatives have been widely used in solid-phase peptide synthesis, and the release of the peptide from the resin can be achieved by 1% TFA in CH_2Cl_2 for 10 min.[10] SASRIN resin has a similar structure

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with Wang resin, except of an *o*-methoxyl group in SASRIN resin. The application of SASRIN–chloride resin to anchor thiols was described;[11] however, to the best of our knowledge, there is no report on the application of SASRIN resin for loading the alcohols. For the development of SPOS, we report here a new SASRIN resin derivative, SASRIN–TOPCAT resin, used for the loading of various alcohols, and the data compared to the known Wang-trichloroacetimidate resin and SASRIN–chloride resin are also discussed (Fig. 1).

The etherification of some SASRIN resin derivatives with alcohol was investigated first. SASRIN–bromide resin was prepared according to the literature.[12] Alcohol **7** was immobilized on it in the presence of NaH, and alcohol **7** was released from the resin by the treatment of 1% TFA in CH_2Cl_2 in 84.9% yield. These results indicated that despite the strong basic conditions for loading, the ether linkage on SASRIN resin can be cleaved under mild conditions. It promoted us to find more mild conditions for the alcohol loading to SASRIN resin. Similar to Wang-trichloroacetimidate resin, SASRIN resin reacted with CCl_3CN in the presence of DBU to give SASRIN–trichloroacetimidate resin rapidly and completely. But in the presence of $BF_3{\cdot}Et_2O$ as a catalyst, alcohols were anchored on SASRIN–trichloroacetimidate resin only in poor yield. After careful examination of the anchoring procedure, it was revealed that $BF_3{\cdot}Et_2O$ could cause partial cleavage of SASRIN–ether linkage even at 0.05 equiv (Scheme 1).

To make the etherification under mild conditions and increase the acid sensitivity of the ether linkage on solid support, SASRIN–2-pyridylthiocarbonate (SASRIN–TOPCAT) resin was prepared according the procedure for the modification of Wang resin. The synthesis of SASRIN–TOPCAT resin from SASRIN resin with di-(2-pyridyl)thiocarbonate under different conditions was investigated, but SASRIN resin was transformed to SASRIN–TOPCAT resin in very poor yield. It was reported that 2-thiopyridyl chloroformate[13] is a more reactive reagent than di-(2-pyridyl)thiocarbonate. Therefore, 2-thiopyridyl chloroformate was reacted with SASRIN resin in the presence of DMAP to give SASRIN–TOPCAT resin successfully. The immobilization of alcohols on SASRIN–TOPCAT resin with AgOTf as a catalyst afforded the moderate yields of resin bearing alcohols (Scheme 2).[14] The loading of various alcohols and thiols on SASRIN–TOPCAT resin is summarized in Table 1.

In our case, the loading of alcohols and thiols to SASRIN–TOPCAT resin was completed in 1–8 h, and the cleavage of the SASRIN–ether linkage and the release of corresponding alcohols were completed efficiently by stir-

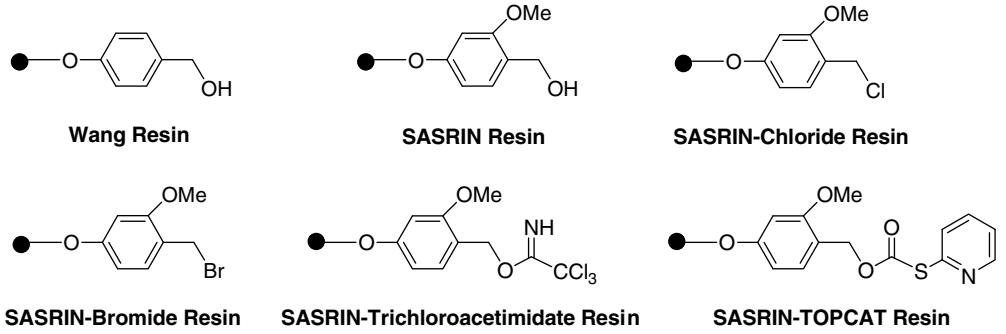
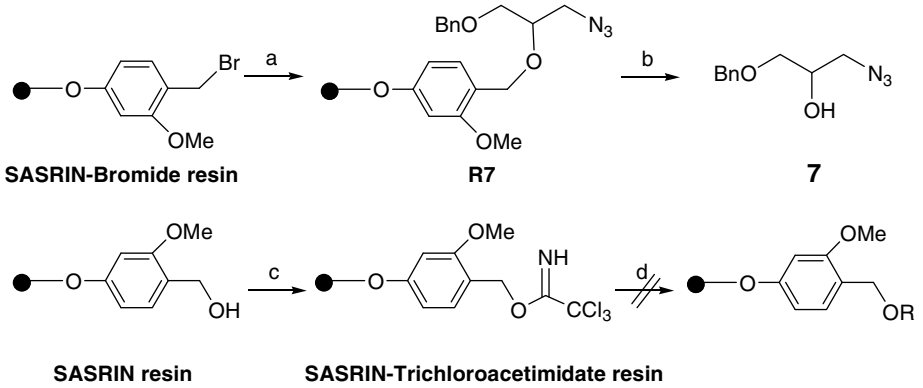
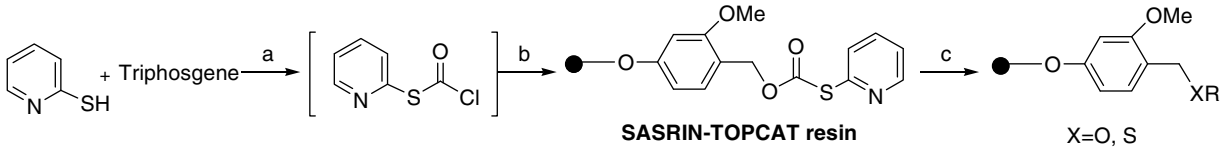


Fig. 1. Structure of Wang resin, SASRIN resin and four SASRIN resin derivatives.

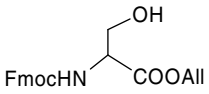
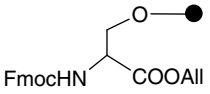
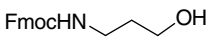
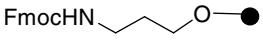
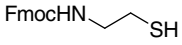
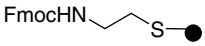
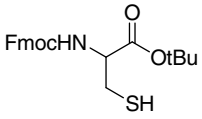
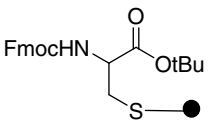
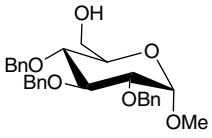
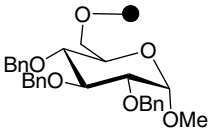
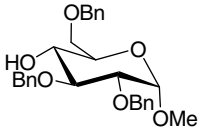
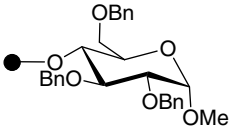
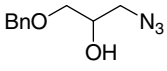
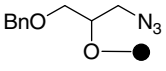
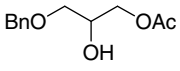
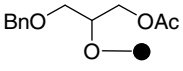


Scheme 1. Alcohol's immobilization on SASRIN–bromide resin and SASRIN–trichloroacetimidate resin. Reagents and conditions: (a) compound **7**, NaH, DMF; (b) 1% TFA/CH_2Cl_2 (5% Et_3SiH was added as scavenger); (c) CCl_3CN, DBU, DCM; (d) ROH, $BF_3{\cdot}Et_2O$, DCM.

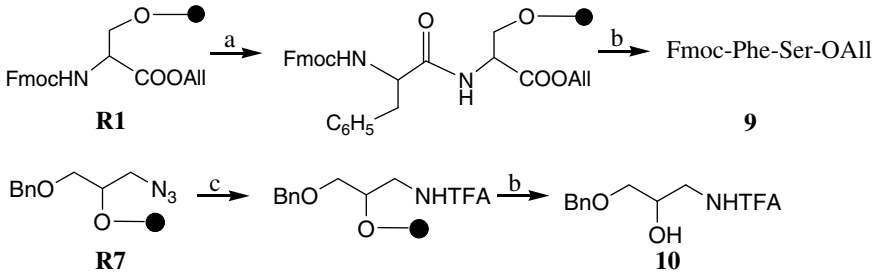


Scheme 2. Preparation of SASRIN–TOPCAT resin and alcohol's immobilization. Reagents and conditions: (a) Et_3N, $PhCH_3$, DCM; (b) SASRIN resin, DMAP, Et_3N, DCM; (c) RXH (X = O, S), AgOTf, DCM.

Table 1
Polymer-bound alcohols and thiols on SASRIN–TOPCAT resin

Alcohols and thiols	Resins	Substitution level (yield)	Substitution level on Wang-trichloroacetimidate resin or SASRIN–chloride resin (yield)[c]
 **1**	 **R1**	0.33 (56.9%)[a]	0.45 (64.3%)[c]
 **2**	 **R2**	0.41 (68.3%)[a]	N.A. (N.A.)[e]
 **3**	 **R3**	0.52 (86.7%)[a]	0.4–0.8 (N.A.)[d]
 **4**	 **R4**	0.44 (78.6%)[a]	0.3–0.6 (N.A.)[d]
 **5**	 **R5**	N.A. (32.6%)[b]	N.A. (N.A.)
 **6**	 **R6**	N.A. (27.9%)[b]	N.A. (N.A.)
 **7**	 **R7**	N.A. (62.6%)[b]	N.A. (N.A.)
 **8**	 **R8**	N.A. (60.2%)[b]	N.A. (N.A.)

[a] Substitution level was determined by the method of Meienhofer through spectrophotometric detection of dibenzofulvene released from SASRIN resin aliquots and was expressed in millimole substrate per gram polystyrene.[18] Yield was based on the percent of maximal theoretical substitution.
[b] Yield was determined by the method reported by Hanessian and Xie.[4]
[c] Substitution was performed on Wang-trichloroacetimidate resin and data were adapted directly from the literature.[19]
[d] Substitution was performed on SASRIN–chloride resin and data were adapted directly from brochure of Bachem A.G.[11]
[e] N.A., no data available



Scheme 3. Synthesis of alcohol derivatives on SASRIN–TOPCAT resin. Reagents and conditions: (a) 20% piperidine/DMF, then Fmoc-Phe-OH, DCC, HOBT, DCM; (b) 1% TFA/CH_2Cl_2 (5% Et_3SiH was added as scavenger); (c) $SnCl_2$/PhSH/Et_3N (1:4:5) in THF, then CF_3COOEt, Et_3N, MeOH.

ring the loading resin in a solution of 1% TFA in CH_2Cl_2 for 15–60 min.[15] To evaluate the efficiency of SASRIN–TOPCAT resin in solid-peptide synthesis, dipeptide Fmoc-Phe-Ser-OAll[16] and 1-*N*-(trifluoroacetyl)-3-(phenylmethoxy)propan-2-ol[17] were also synthesized on SASRIN–TOPCAT resin in 91.6% and 47.1% yield, respectively (Scheme 3).

SASRIN–TOPCAT resin has some advantages compared to the current solid supports. The first one lies on the more acid-sensitive ether linker in SASRIN–TOPCAT resin than the ether linker in Wang resin or the acetal linker in dihydropyranyl (DHP) resin. Second, SASRIN–TOPCAT resin is stable at room temperature in a desiccator after one month. It also exhibits the relative high loading capability and yields for the peptide synthesis. Finally, as shown in Table 1, SASRIN–TOPCAT resin can be used in the loading of various alcohols or thiols substrates, and the side reactions, such as N-alkylation, ester migration, β-elimination or epimerization were not observed.

In conclusion, a new SASRIN resin derivative, SASRIN–TOPCAT resin, was synthesized and this new resin can be used for the loading of alcohols and thiols under neutral conditions, and the release of alcohol from the resin is achieved by the treatment of 1% TFA in CH_2Cl_2 for 15–60 min. Compared to the other reported resins, SASRIN–TOPCAT resin is more suitable for the loading of alcohols in solid-phase organic synthesis.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.017.

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14. Preparation of SASRIN–2-pyridylthiocarbonate resin (SASRIN–TOPCAT resin): Starting from triphosgene (12.00 g, 40.4 mmol), 2-thiopyridyl chloroformate was obtained according to Corey's procedure and used in situ without further purification. The flask was rinsed with an additional volume of CH_2Cl_2 (20 mL) and Et_3N (3.6 mL, 25.8 mmol). SASRIN resin (2.00 g, 0.76 mmol/g) and DMAP (170 mg, 0.14 mmol) were added at 0 °C and agitated for 24 h. The resin was washed with H_2O, MeOH and CH_2Cl_2 successively and dried in high vacuum to give SASRIN–TOPCAT resin (theoretical maximal substitution level 0.68 mmol/g). FT-IR (KBr pellet) 3397, 3081, 3059, 3025, 2923, 2852, 1946, 1875, 1804, 1722 (C=O), 1612, 1587, 1508, 1494, 1451, 1420, 1373, 1333, 1288, 1197, 1107, 1031, 907, 821, 757, 698, 665, 618, 538, 484 cm^{-1}.
15. General procedure for the loading and the cleavage of alcohols to SASRIN–TOPCAT resin: The alcohol (3 equiv) was added to a suspension of the resin (200 mg) in CH_2Cl_2 (4 mL), and AgOTf (3 equiv) was added in one portion. After agitated for 1–8 h in dark, the resin was quenched with pyrimidine for another 30 min and filtered, washed with CH_2Cl_2, DMSO, MeOH, CH_2Cl_2 and dried in high vacuum. Alcohols were cleaved by 1% TFA in CH_2Cl_2 (5% Et_3SiH was added as scavenger) for 15–60 min. *Note*: Cleavage of thiols from SASRIN resin required more harsh acid conditions. 50%

TFA in CH_2Cl_2 was recommended which had been reported by Bachem A.G. But *tert*-butyl ether in compound **4** was also partially cleaved at this acid conditions. For more detailed information, see: http://www.bachem.com.

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