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Solid-Phase Synthesis of Anagrelide Sulfonyl Analogues

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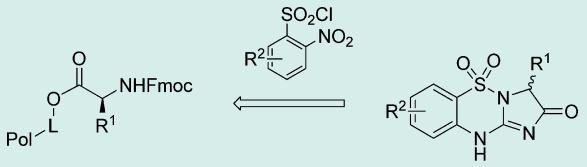
Supporting Information

ABSTRACT: Simple solid-phase synthesis of 3,10-dihydro-2*H*-benzo[e]imidazo[1,2-*b*][1,2,4]thiadiazin-2-one 5,5-dioxides is described, with Fmoc-*α*-amino acids and 2-nitrobenzenesulfonyl chlorides (2-NosCls) being the key building blocks. Fmoc-*α*-amino acids were immobilized on Wang resin and transformed to the corresponding 2-nitrobenzenesulfonamides in two steps. After reduction of the nitro group, Fmoc-thioureas were synthesized followed by cyclization of the 1,2,4-benzothiadiazine-1,1-dioxide scaffold with diisopropylcarbodiimide (DIC). Cleavage of the Fmoc protecting group followed by spontaneous cyclative cleavage gave the target products in excellent crude purity.



KEYWORDS: *anagrelide analogues, cyclic guanidines, Fmoc-amino acids, 2-nitrobenzenesulfonyl chlorides, solid-phase synthesis, cyclative cleavage*

INTRODUCTION

2-Nitrobenzenesulfonyl chloride (2-NosCl) and 4-nitrobenzenesulfonyl chloride (4-NosCl) are frequently used reagents in organic synthesis. They have typically been used for the preparation of the corresponding nitrobenzenesulfonamides which allows monoalkylation of a primary amino group with use of either alkyl halides or alcohols.[1] After alkylation, the nitrobenzenesulfonyl group can be smoothly removed by treatment with ethanethiol/DBU cleavage cocktail. In our previous research, we used this strategy for the preparation of some benzodiazepinones[2] (use of 2-NosCl) or tetrahydrobenzodiazepinones[3] (use of 4-NosCl). Alternatively, 2-NosCl and 4-NosCl can be used as common building blocks for small molecules synthesis. Quite recently Krchnak et al. reported an interesting synthetic pathway leading to indazol derivatives via polymer supported *N*-(2-nitrobenzenesulfonyl)-amino acids.[4,5] Inspired by this contribution we proposed the use of *N*-(2-nitrobenzenesulfonyl)-*α*-amino acids) for the preparation of 3,10-dihydro-2*H*-benzo[e]imidazo[1,2-*b*][1,2,4]thiadiazin-2-one 5,5-dioxides (Figure 1). The target scaffold was initially synthesized in 2010 by Saito et al. with use of traditional solution-phase synthesis (Scheme 1).[6]

The single published strategy is based on aza-Wittig reaction using iminophosphoranes as the key synthons, prepared from 2-azidobenzenesulfonyl chlorides and *α*-amino acids methyl esters. While being efficient, this synthetic approach relies on the somewhat problematic availability of starting azidobenzenesulfonyl chlorides, and also relies on purification by silica gel chromatography throughout the reaction sequence. Biological properties of 3,10-dihydro-2*H*-benzo[*e*]imidazo[1,2-*b*][1,2,4]-thiadiazin-2-one 5,5-dioxides have never been reported, but the structure is very closely related to Anagrelide (Agrylid/Xagrid),[7,8] a drug used for the treatment of essential thrombocytosis,[9,10] overproduction of blood platelets and chronic meyloid leukemia (Figure 1).[11]

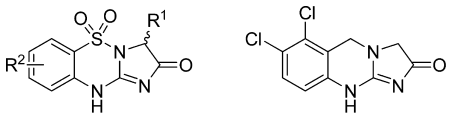
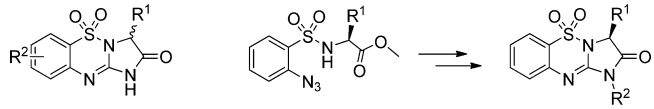


Figure 1. General structure of target compounds and Anagrelide.

Scheme 1. Target Scaffold and Synthesis of Analogueical Compounds by Saito et al.



Because of this similarity, we presumed promising pharmacological properties of the target compounds and we focused on the development of a convenient and modular solid-phase[12] method for the preparation of libraries to study potential structure−activity relationships. To make the methodology generally applicable, we used only commercially available building blocks and common coupling reagents and procedures. A key element is the cyclative release of the completed products from the synthesis resin at the last step.

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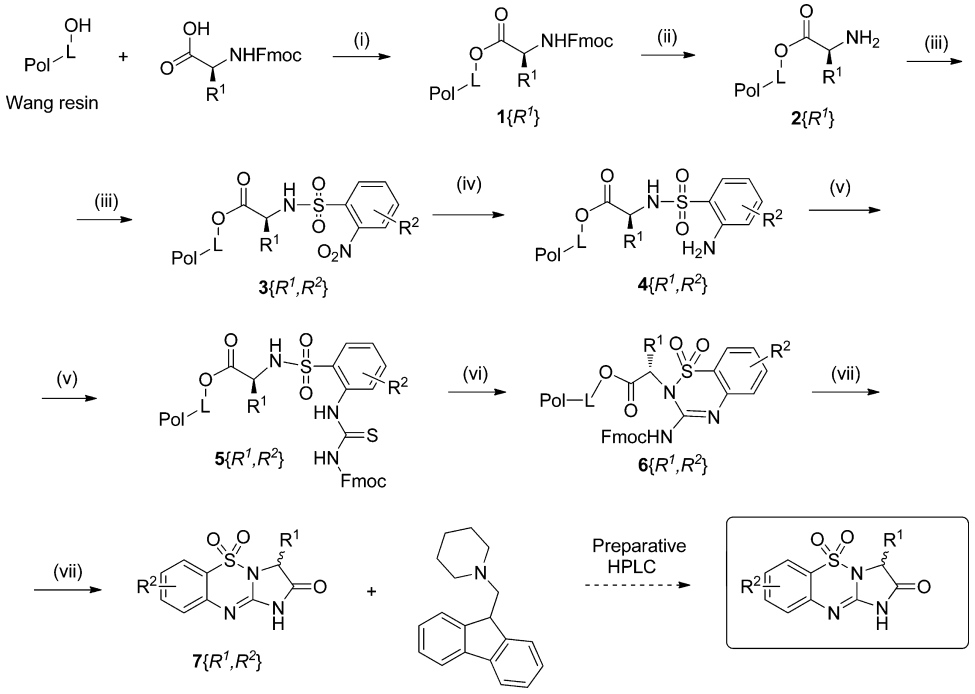
Scheme 2. Synthetic Pathway Leading to Target Compounds[a]



[a]Reagents and conditions: (i) Fmoc-amino acid, DIC, HOBt, DMAP, DCM, DMF, rt, overnight; (ii) piperidine, DMF, rt, 30 min; (iii) 2-nitrobenzenesulfonyl chloride, 2,6-lutidine, DCM, rt, overnight; (iv) sodium dithionite, potassium carbonate, TBAHS, water, rt, 2 h; (v) Fmoc-NCS, THF, rt, overnight; (vi) DIC, DMF, rt, overnight; (vii) piperidine, DMF, rt, 30 min.

RESULTS AND DISCUSSION

The general synthetic approach is shown in Scheme 2. The first two steps are based on traditional solid-phase peptide synthesis using Wang resin and Fmoc-α-amino acids. To verify the synthetic route, Wang resin was acylated with Fmoc-L-Ala-OH followed by cleavage of the Fmoc protecting group with piperidine. The intermediate **2**{*2*} was reacted with 2-nitrobenzenesulfonyl chloride and subsequently the nitro group of sulfonamide **3**{*2,1*} was reduced using the sodium dithionite method reported recently.[13] Reaction of **4**{*2,1*} with Fmoc-NCS gave the corresponding Fmoc-thiourea **5**{*2,1*} which after treatment with DIC, furnished intermediate **6**{*2,1*} in excellent crude purity (96%, calculated from LC/UV traces). Cleavage of the Fmoc protecting group was followed by spontaneous intramolecular aminolysis of ester bond and the target product 7{*2,1*} was released from the polymer support by a cyclative cleavage.[14] Separation of the product from the fluorenylmethylpiperidine byproduct formed after Fmoc protecting group removal was easily accomplished by reverse phase semipreparative HPLC. The model compound 7{*2,1*} was obtained in a very good overall yield of 45%.

To evaluate the scope and limitations of our method we selected representative building blocks with variable electronic and steric properties: five 2-nitrobenzenesulfonyl chlorides with electron-donating or electron-withdrawing ligands were tested, as well as four Fmoc-amino acids with different substitution of a side chain (Figure 2). With use of the split-and-split method[12] and polypropylene fritted syringes, we prepared the full 4 × 5 library of 20 compounds. The purities of crude intermediates **6**{R^1,R^2} ranged from 63% to 98% and the final compounds were obtained in good overall yields (Table 1).

In addition, we investigated the possible use of the reaction sequence for the preparation of N^1-substituted derivatives of

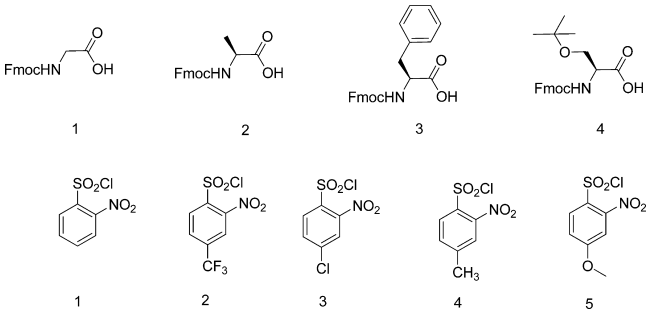


Figure 2. Building blocks successfully used for verification of the synthetic route.

compounds 7 by replacing Fmoc-NCS with benzyl-NCS. Surprisingly the reaction with **4**{*2,1*} did not take place, even at elevated temperature. Benzyl-NCO provided the intermediate **10** in excellent purity but unfortunately the following cyclization with DIC was not successful (Scheme 3) and only the starting material was recovered. When the resin **10** was heated to reflux in toluene, the compound decomposed to give only a mixture of unknown compounds.

In the preparation of 5-noranagrelide derivatives based on a similar solid-phase approach we observed complete racemization of the single stereocenter.[15] For this reason, we evaluated the effect of the cyclization reaction on the potential racemization of 7{R^1,R^2} by synthesizing compound 7^{DL}{*2,1*} from an equimolar mixture of Fmoc-D-Ala-OH and Fmoc-L-Ala-OH. The compounds 7^{DL}{*2,1*} and 7{*2,1*} were subjected to chiral HPLC analysis (Chiralpak IF column), revealing that partial racemization occurred (enantiomer ratio 62:38, Supporting Information) during the synthesis of 7{*2,1*} from the enantiopure starting material. The effect of the stereocenter

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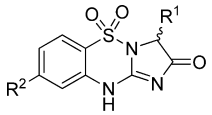
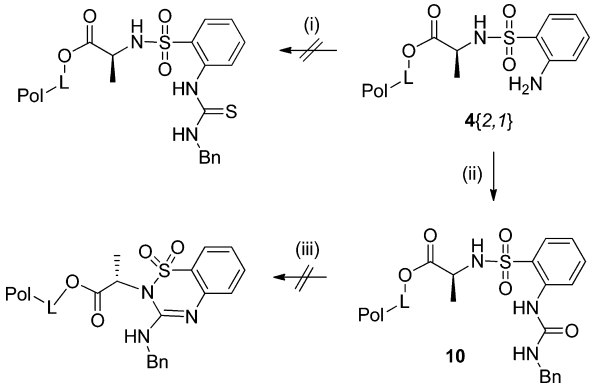
Table 1. List of Prepared Compounds 7{R^1,R^2}



compound	R^1	R^2	crude purity[a]	yield[b] (%)
7{1,1}	H	H	90	69
7{1,2}	H	CF_3	92	22
7{1,3}	H	Cl	70	14
7{1,4}	H	Me	98	22
7{1,5}	H	OMe	85	10
7{2,1}	Me	H	96	45
7{2,2}	Me	CF_3	91	34
7{2,3}	Me	Cl	98	26
7{2,4}	Me	Me	93	35
7{2,5}	Me	OMe	98	36
7{3,1}	CH_2Ph	H	64	24
7{3,2}	CH_2Ph	CF_3	65	28
7{3,3}	CH_2Ph	Cl	72	35
7{3,4}	CH_2Ph	Me	92	33
7{3,5}	CH_2Ph	OMe	63	43
7{4,1}	CH_2OtBu	H	70	36
7{4,2}	CH_2OtBu	CF_3	90	47
7{4,3}	CH_2OtBu	Cl	93	16
7{4,4}	CH_2OtBu	Me	87	62
7{4,5}	CH_2OtBu	OMe	98	40

[a]Crude purity of precursors 6{R^1,R^2} after cleavage from the polymer support calculated from LC-UV traces (215 nm). [b]Overall yields after six steps and preparative HPLC purification calculated from loading of Fmoc amino acids (resins **1**).

Scheme 3. Attempt to Increase Diversity of Target Compounds: N^1 Substitution.[a]



[a]Reagents and conditions: (i) Bn-NCS, THF, rt or 50 °C, overnight; (ii) Bn-NCO, THF, rt, overnight; (iii) DIC, DMF, rt to 50 °C, overnight or toluene, reflux, overnight.

substitution (different R^1 ligands) and reaction conditions on the resulting stereochemistry will be studied in the near future.

In conclusion, we have developed a convenient high-throughput synthesis of Anagrelide sulfonyl analogues with two diversity positions based on solid-phase chemistry on Wang resin. The reaction sequence can be accomplished in 4 days with only ca. 60 min total hands-on time. Various building blocks were tested and a model library of 20 compounds was prepared and fully characterized. The target substances were isolated in good overall yields. Since a number of building blocks (particularly Fmoc-amino acids, both natural and non-natural) are commercially available, the developed method can be applied for the simple preparation of sizable chemical libraries of this privileged molecular scaffold.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of experimental synthetic and analytical procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Fukuyama, T.; Jow, Ch.-K.; Cheung, M. 2- and 4-Nitrobenzenesulfonamides: Exceptionally Versatile Means for Preparation of Secondary Amines and Protection of Amines. *Tetrahedron Lett.* **1995**, *36* (36), 6373−6374.

(2) Fulopova, V.; Gucky, T.; Grepl, M.; Soural, M. Solid-Phase Synthesis of Trisubstituted Benzo[1,4]-Diazepin-5-one Derivatives. *ACS Comb. Sci.* **2012**, *14* (12), 651−656.

(3) Lemrova, B.; Soural, M. Solid-Phase Synthesis of 4,7,8-Trisubstituted 1,2,3,4-Tetrahydro-benzo[*e*][1,4]diazepin-5-ones. *ACS Comb. Sci.* **2012**, *14* (12), 645−650.

(4) Pudelova, N.; Krchnak, V. Efficient Traceless Solid-Phase Synthesis of 3,4-Dihydropyrazino[1,2-*b*]indazoles and Their 6-Oxides. *J. Comb. Chem.* **2009**, *11* (3), 370−374.

(5) Bouillon, I.; Zajicek, J.; Pudelova, N.; Krchnak, V. Remarkably Efficient Synthesis of 2*H*-Indazole 1-Oxides and 2*H*-Indazoles via Tandem Carbon−Carbon Followed by Nitrogen−Nitrogen Bond Formation. *J. Org. Chem.* **2008**, *73* (22), 9027−9032.

(6) Hirota, S.; Sakai, T.; Kitamura, N.; Kubokawa, K.; Kutsumura, N.; Otani, T.; Saito, T. Synthesis of Nitrogen Heterocycle-Fused 1,2,4-Benzothiadiazine-1,1-dioxide, Quinazolinone, and Pyrrolidinone Derivatives with a Guanidine Joint via Sequential aza-Wittig Reaction/Intramolecular NH-Addition Cyclization/Nucleophilic Substitution Ring Closure Methodology, Using Functionalyzed Carbodiimides As Key Intermediates. *Tetrahedron* **2010**, *66* (3), 653−662.

(7) *The Merck Index*, 11th ed.; Merck: Rahway, NJ, U.S.A., 1989; p 98.

(8) Fleming, J. S.; Buyniski, J. P. A Potent New Inhibitor of Platelet Aggregation and Experimental Thrombosis, Anagrelide (BL-4162A). *Thromb. Res.* **1979**, *15* (3−4), 373−388.

(9) Reilly, J. T. Anagrelide for the Treatment of Essential Thrombocythemia: A Survey among European Hematologists/Oncologists. *Hematology* **2009**, *14* (1), 1−10.

(10) Pescatore, S. L.; Lindley, C. Anagrelide: A Novel Agent for the Treatment of Myeloproliferative Disorders. *Expert Opin. Pharmacother.* **2000**, *1* (3), 537−546.
(11) Trapp, O. M.; Beykirch, M. K.; Petrides, P. E. Anagrelide for Treatment of Patients with Chronic Myelogenous Leukemia and a High Platelet Count. *Blood Cells, Mol. Dis.* **1998**, *24* (1), 9−13.
(12) Hlaváč, J.; Soural, M.; Krchňák, V. In *Solid-Phase Organic Synthesis*; Toy, P. H., Lam, Y., Eds.; Wiley: Hoboken, NJ, U.S.A., 2012, 95−130.
(13) Kaplánek, R.; Krchňák, V. Fast and Effective Reduction of Nitroarenes by Sodium Dithionite under PTC Conditions: Application in Solid-Phase Synthesis. *Tetrahedron Lett.* **2013**, *54* (21), 2600−2603.
(14) Ganesan, A. Cyclative Cleavage as the Solid-Phase Strategy. In *Linker Strategies*; Scott, P. J. H., Ed.; Wiley: Chichester, West Sussex, U.K., 2012; p 135.
(15) Messina, I.; Popa, I.; Maier, M.; Soural, M. Solid-Phase Synthesis of 5-Noranagrelide Derivatives. *ACS Comb. Sci.* **2014**, *16* (1), 33−38.