Pergamon

Tetrahedron Letters 41 (2000) 5971–5974

TETRAHEDRON LETTERS

A novel isoxazole-based scaffold for combinatorial chemistry[1]

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Received 13 April 2000; accepted 7 June 2000

Abstract

A novel isoxazole-based scaffold has been identified for the generation of combinatorial libraries using solid-phase methods. This scaffold has been utilized to afford high value synthetic intermediates through Baylis–Hillman reaction, Wittig reaction, nitroaldol condensation, and imine and oxime formation. The utility of the scaffold has been demonstrated by synthesizing a small library of 32 isoxazole substituted γ-amino alcohol using four activated alkenes and eight amines. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: combinatorial chemistry; 5-isoxazolecarboxaldehyde; SPOS; Baylis–Hillman reaction; Wittig reaction.

The construction of diverse multifunctional libraries of small organic molecules on solid supports has been the most important feature of the evolution of combinatorial chemistry in the recent years.[2] This approach has led to the syntheses of various biologically active molecules such as benzodiazepines, hydantoins, dihydro-pyridines, pyridines, benzopyrazones, ureas, sulfonamides, carbamates, lactams, xanthines, oxazolones, sugar analogs, etc. both in parallel format or when using the split and mix method.[3] Despite this enormous development, much of the solid-phase synthesis is indeed a direct translation of known solution-phase chemistry to obtain large numbers of possible analogs of a bioactive molecule. The isoxazole ring system that can be easily obtained by [3+2] cycloadditions of nitrile oxides with acetylenes is of particular interest since it is a component of various pharmaceutical agents and also a precursor to useful synthetic intermediates such as γ-amino alcohols and β-hydroxy ketones. Though the synthesis of isoxazoles on 2-chlorotrityl resin has been described earlier using the above-mentioned synthetic strategy no further work on its chemistry is reported on solid-phase.[4] In our efforts towards exploring the chemistry of isoxazoles on solid-phase we observed that 3-(4-hydroxy-phenyl)-5-isoxazolecarboxaldehyde can serve as a good scaffold for obtaining structurally diverse derivatives of isoxazoles. The details of this study are presented here.

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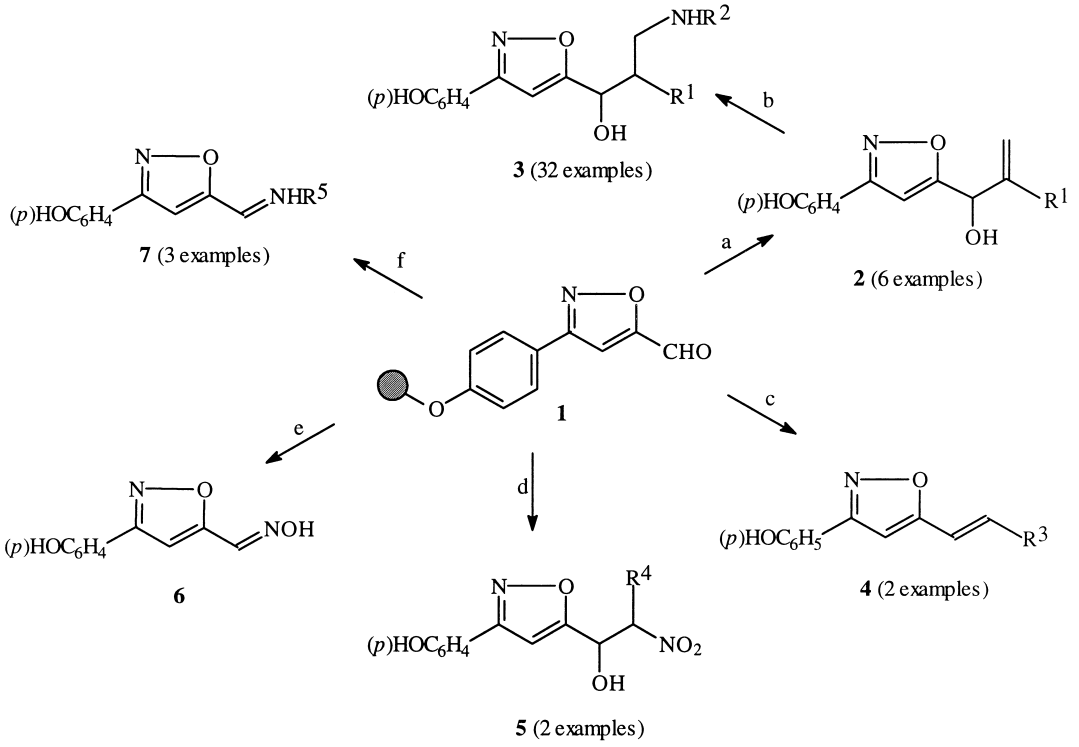
PII: S0040-4039(00)00951-5

The solid-phase synthesis of various isoxazole derivatives using 3-(4-hydroxyphenyl)-5-isoxazolecarboxaldehyde as a novel scaffold has been outlined in Scheme 1. Cleavage of numerous 5–7 mg samples of the resin bound intermediates with subsequent HPLC, FAB MS and PMR of the resultant products accompanied each step during optimization.



Scheme 1. a) $CH_2=CHR^1$, DABCO, DMSO, rt, 1 h; b) R^2NH_2 or *N*-methylpiperazine, DMF, 50°C, 12 h; c) $PPh_3CH_2R^3X$, NaOMe, THF/MeOH, 60°C, 6 h; d) $R^4CH_2NO_2$, EtOH/THF, rt, 3 h; e) $NH_2OH.HCl$, pyridine, rt, overnight; f) R^5NH_2, TMOF, 3 h

The 3-(4-hydroxyphenyl)-5-isoxazolecarboxaldehyde used as starting material for the present study was obtained from debenzylation of the corresponding benzyloxy substituted aldehyde in the presence of acetic acid:HCl mixture (2:1, v/v). In the first step the 3-(4-hydroxyphenyl)-5-isoxazolecarboxaldehyde was loaded onto 2-chlorotrityl resin (1.4 mmmol/gm) in the presence of DIEA and DMAP mixture in DMF at 50°C for 12 h. The loading was determined by HPLC after cleavage and was found to be 1.3 mmol/gm (loading ~93%). Since it had been observed earlier that these aldehydes are excellent substrates for fast Baylis–Hillman reaction in solution phase,[5] the first synthetic strategy involved an adoption of the same approach on the solid-phase. Treatment of the resin bound 5-isoxazolecarboxaldehyde with a mixture of DABCO and an activated alkene in DMSO led to formation of Baylis–Hillman adducts **2** within 1 h in excellent yield and purity.[6] This is in contrast to solid-phase Baylis–Hillman reactions reported in the literature where alkenes are normally anchored onto the solid support and are then treated with various aldehydes.[7,8] In addition, the reaction rates reported for these reactions are usually slow and yields are invariably moderate even after double coupling. Our findings thus constitute the

first report of anchoring the aldehyde on to the solid support and utilizing structurally diverse activated alkenes for carrying out the Baylis-Hillman reaction.

Further, to investigate the scope and limitation of the scaffold, nitro aldol condensation with nitromethane and nitroethane, Wittig reaction with triphenyl phosphonium methylene iodide and triphenyl phosphonium bromoethyl acetate, imine formation with various amines and oxime formation with hydroxylamine hydrochloride were carried out to obtain numerous versatile intermediates **4**, **5**, **6** and **7**, respectively. The compounds **4**, **6** and **7** were obtained as mixtures of geometrical isomers, whereas compounds **5** were obtained as diastereomeric mixtures. The purities of these compounds ranged from 70–95% based on analytical HPLC.

These intermediates are indeed good substrates for developing the isoxazole-based libraries. This has been demonstrated by carrying out synthesis of a small library of 32 isoxazole-substituted γ-amino alcohols **3** in parallel format by using four activated alkenes and eight amines. The chemical steps involved in the synthesis of **3** are the formation of a Baylis–Hillman adduct followed by a Michael addition of amines to the double bond of the intermediate **2**. After optimizing the reaction conditions in syringes, the library was generated through automation on an Advanced Chemtech 496Ω Multiple Organic Synthesizer. The Michael adducts were obtained as diastereomeric mixtures in good yields with purities ranging from 65–90% (Table 1).

Table 1
Structures, yields and purity of the representative compounds

Compound		R	Yield	Purity
2a		CO_2Et	95	97
3b	R^1,R^2	CO_2Et , $CH_2CH_2NEt_2$	82	91
	R^1,R^2	$CO_2{}^tBu$, CH_2Ph	71	76
	R^1,R^2	CO_2Et , CH_2CH_2-(pyrrolidin-1-yl)	65	69
	R^1,R^2	CO_2Et , (4-methyl-piperazin-1-yl)	97	94
	R^1,R^2	CO_2Bu , CH_2CH_2-(piperazin-4-yl)	81	73
	R^1,R^2	CN, CH_2-(furan-2-yl)	78	81
	R^1,R^2	CO_2Et , CH_2-(piperidin-4-yl)	72	70
	R^1,R^2	CO_2Bu , CH_2CH_2-(morpholin-4-yl)	70	75
4	R^3	H	76	85
5	R^4	H	96	95
7	R^5	CH_2Ph	79	91

In summary, we have identified 3-(4-hydroxyphenyl)-5-isoxazolecarboxaldehyde as a novel building block for the generation of isoxazole-based libraries. This has been exemplified by successfully synthesizing various useful synthetic intermediates, which can be further diversified to get an array of isoxazole-based novel compounds. The 32-member library of isoxazole-substituted 1,3-aminoalcohols reported herein is being evaluated in several in vitro assays for the generation of new leads. The synthetic potential of this novel scaffold is being explored further to generate novel heterocyclic compounds.

Acknowledgements

The financial support to S.K.R. from the Director (CDRI), and A.P. from Volkswagen (Germany), respectively, in the form of a fellowship is gratefully acknowledged.

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6. **General procedures**. *Baylis–Hillman reaction*: To the resin loaded with aldehyde (50 mg) in DMSO (250 μL) was added a 15 min premixed solution of DABCO (2.5 equivalents) and alkene (5 equivalents) in DMSO (250 μL) and the reaction was shaken at 600 rpm for 1 h. Thereafter the resin was sequentially washed with DMF, MeOH, DCM and ether (5×3 ml each) and dried. The resin was cleaved with 5% TFA in DCM for 20 min. After evaporation of TFA solution under vacuum, *tert*-butanol:water mixture (4:1, v/v) was added to the residue and freeze dried to obtain the product **2**. [$R^1 = CH_2CH_3$: FAB MS 289(M^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, $J = 7$ Hz, CH_3), 3.73 (br s, 1H, OH), 4.20 (q, 2H, $J = 7$ Hz, CH_2), 5.73 (s, 1H, CHOH), 6.13, 6.44 (2s, 2H, 1H each of $=CH_2$), 6.46 (s, 1H, =CH), 6.89 (d, 2H, $J = 9$ Hz, Ar-H), 7.62 (d, 2H, $J = 9$ Hz, Ar-H), 8.95 (brs, 1H, Ar4-OH)]. *Michael addition*: To the resin (50 mg) in DMF (500 μL) was added amine (10 equivalents) and the reaction was stirred at 50°C for 12 h. The resin was sequentially washed, cleaved and lyophilized as mentioned above to obtain the amino derivatives. [$R^1 = CH_2CH_3$, NHR^2 = (4-methyl-piperazin-1-yl); FAB MS 389 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 1.22 (t, 6H, $J = 7$ Hz, $2\times CH_3$), 2.63 (s, 6H, $2\times CH_3$), 2.79 (m, 20H, $10\times CH_2$), 3.16 (m, 2H, 2×CH), 4.18 (q, 4H, $J = 7$ Hz, $2\times CH_2$), 5.18 (m, 1H, CH), 5.23 (m, 1H, CH), 6.51 (s, 2H, 2×CH), 6.92 (d, 4H, $J = 9$ Hz, Ar-H), 7.61, 7.64 (d, 4H, $J = 9$ Hz, Ar-H). *Wittig reaction*: To the resin loaded with aldehyde (50 mg) in THF (400 μL) was added triphenyl phosphonium methyl iodide (5 equivalents) and solution of NaOMe (6 equivalents) in MeOH (100 μL) and the reaction was stirred at 60°C for 6 h. Thereafter the resin was sequentially washed with 50% aq. MeOH (10×4 mL), MeOH and ether (6×4 mL). The resin was cleaved and freeze dried as mentioned above to obtain the product. *Nitroaldol condensation reaction*: To the resin loaded aldehyde (50 mg) in THF (200 μL) was added nitromethane (30 equivalents), ethanol (30 equivalents) and triethylamine (15 equivalents) and the reaction was shaken at 800 rpm for 3 h. Thereafter the resin was washed with THF, DMF, MeOH, DCM and ether (5×3 mL each). The cleavage of resin and freeze-drying of the residue was performed as mentioned above.
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