Synthesis of Boron-containing Passerini Analogues and their Biological Evaluations

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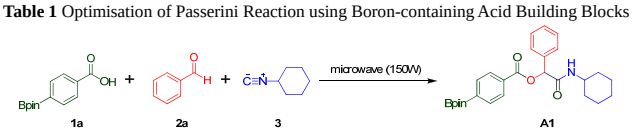
Introduction

In this report, a Passerini three-component reaction utilizing boron-containing carboxylic acids or aldehydes is discussed. The reaction was carried out in water and facilitated by the use of microwave irradiation. This methodology allowed for the efficient formation of a broad range of boron-containing α-acyloxyamides under mild conditions within a short time. Two series of boron-containing α-acyloxyamides were synthesized and subsequently screened for cytotoxicity using the MTT cell viability assay. Two potential lead compounds were found to have potent activity against the HepG2 cancer cell line, demonstrating the potential of this methodology for use in the development of novel pharmaceuticals.

Results and Discussion

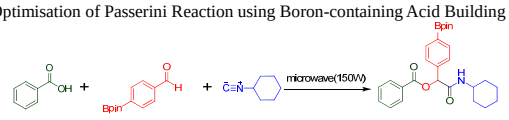
Table 1 Optimisation of Passerini Reaction using Boron-containing Acid Building Blocks



Enrty	Temp. (° C)	Solvent	Conc. (M)	Time (min)	Yields (%)
1	45° C	DCM	0.25	90	N.R.
2	45° C	MeOH	0.25	90	N.R.
3	45° C	THF	0.25	90	39
4	45° C	H_2O	0.25	90	77
5	45° C	H_2O	1	90	84
6	45° C	H_2O	1	120	88
7	55° C	H_2O	1	120	N.D. [a]
8	55° C	H_2O	1	1day	69 [b]

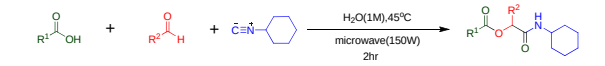
[a] The decomposition of the product was observed; [b] Reaction performed without microwave irradiation.

Table 2 Optimisation of Passerini Reaction using Boron-containing Acid Building Blocks



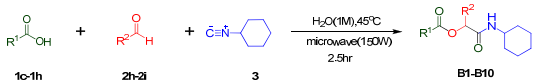
Enrty	Temp. (° C)	Solvent	Conc. (M)	Time (min)	Yields (%)
1	45 ° C	H_2O	0.25	90	N.R.
2	45 ° C	H_2O	1	90	58
3	45 ° C	H_2O	1	120	65
4	45 ° C	H_2O	1	150	75
5	45 ° C	H_2O	1	210	60

Table 3 Synthesis of Passerini Products with Boron-containing Acid Building Blocks



Enrty	R^1	R^2	Product	Yields(%)
1	(1a)	(2a)	A1	88
2	(1b)		A2	83
3		(2b)	A3	76
4			A4	79
5		(2c)	A5	87
6			A6	79
7		(2d)	A7	56
8			A8	52
9		(2e)	A9	57
10			A10	63

Table 4 Synthesis of Passerini Products with Boron-containing Aldehyde Building Blocks



Enrty	R^1	R^2	Product	Yields(%)
1	(1d)	(2h)	B1	75
2		(2i)	B2	69
3	(1e)		B3	57
4			B4	59
5	(1f)		B5	72
6			B6	63
7	(1g)		B7	80
8			B8	82
9	(1h)		B9	85
10			B10	89

Conclusion

In conclusion, a convenient and efficient microwave-assisted Passerini MCR under aqueous conditions was developed. A broad range of boron-containing α-acyloxyamides were synthesized in moderate to good yields using this method. In addition, a simple acid/base extraction protocol was developed, which enabled simple and effective purification of these boron-containing compounds. This is a major achievement that renders this synthetic strategy suitable for use in the library synthesis of boron molecules. All of the synthesized analogs were screened using the MTT assay, with two compounds found to be active against the HepG2 cell line. Further structure–activity relationship evaluations based on these two analogs is currently ongoing, and the results will be reported in due course.

Acknowledgements

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