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Tetrahedron Letters 45 (2004) 313–316
Tetrahedron Letters

Smart cleavage reactions: the synthesis of benzimidazoles and benzothiazoles from polymer-bound esters ☆

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Received 8 October 2003; revised 27 October 2003; accepted 28 October 2003

Abstract—The preparation of an array of benzimidazoles and benzothiazoles from polymer-bound esters is described. Polymer-bound esters were treated with 2-aminothiophenols or 1,2-phenylenediamines in the presence of a Lewis acid to afford the corresponding benzothiazole or benzimidazole cleavage products. The reaction of 2-aminophenols with the polymer-bound esters failed to give the desired benzoxazole products using this procedure.

1. Introduction

Combinatorial chemistry is now the accepted method of choice for the preparation of chemical libraries for screening in drug discovery programs.[1] Solid-phase synthesis[2] is especially useful in library production since large numbers of compounds can be generated using only a few separate reactions during a 'split-and-mix' synthesis.[3] The choice of linker for the library scaffold to the polymer support is critical for successful library production,[4] and a number of groups have devised elegant methods that enable additional diversity to be incorporated into the products during the cleavage reaction. For example, Ley and later Morphy demonstrated that polymer-bound esters could be cleaved from the resin by reaction with an amine in the presence of Lewis acid to provide the corresponding amide products.[5] We have utilized this cleavage methodology to produce amide-functionalized oxazole,[6] indole,[7] and imidazolone[8] libraries that were prepared from polymer-bound α-diazo-β-ketoesters as key intermediates.[9] We investigated the use of a diverse selection of amine building blocks in this cleavage/diversification reaction and an interesting observation was made when 2-aminothiophenol **2** was reacted with polymer-bound oxazole **1** in the presence of $AlMe_3$. In this instance, instead of the anticipated amide product **3**, the cyclo-dehydrated benzothiazole **4** was isolated as the major product from this reaction (Fig. 1).

Although there are several reports for the direct conversion of esters into the corresponding benzimidazoles and benzothiazoles, these reactions required extremely harsh conditions and often the products were isolated in poor yields.[10] However, there have been two reports whereby this transformation was performed under milder, Lewis acid promoted conditions; this corroborated our observation of the fully dehydrated benzothiazole product **4**, rather than the expected amide **3**.[11] Accordingly, we set out to extend the application of this reaction toward its use as a diversity-building cleavage reaction from the solid support. Reported herein are our findings from these investigations.

The first set of reactions was performed in order to establish the effect of the type of Lewis acid and the ratio of amino substrate **7** to Lewis acid upon the success of

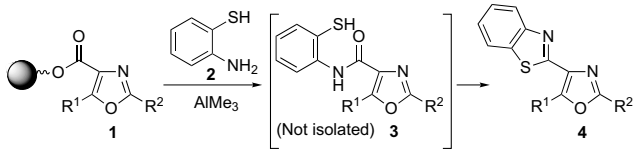

Figure 1. Unexpected formation of a benzothiazole cleavage product.

Keywords: Solid-phase; Cleavage; Lewis acid; Heterocycles.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.10.168.

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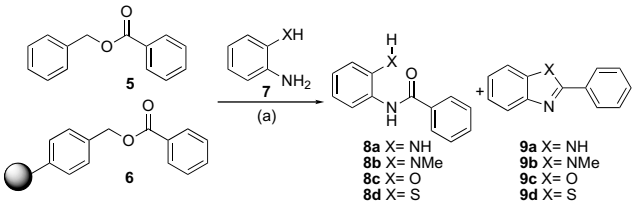
doi:10.1016/j.tetlet.2003.10.168

the reaction. In order to expedite this study, benzyl benzoate **5** was used as a model solution-phase analogue of a hydroxymethyl *J*anda*J*el[12] resin-supported ester **6**,[13] (Scheme 1, Table 1).

Four amines **7** were tested in this reaction, 1,2-phenylenediamine (X = NH), *N*-methyl-1,2-phenylene diamine (X = NMe), 2-aminophenol (X = O) and 2-aminothiophenol (X = S). Of the Lewis acids examined, trimethylaluminum ($AlMe_3$) and diethylaluminum chloride (Et_2AlCl) provided the best results, whereas aluminum chloride ($AlCl_3$) was rejected early in this study since it only gave complex mixtures of cleaved compounds with poor mass recovery. More precisely, when X = NH, Et_2AlCl was found to be superior to $AlMe_3$, and when



Scheme 1. Reagents and conditions: (a) Lewis acid, toluene, reflux, 24 h.

Et_2AlCl was used at a substrate/reagent ratio (ester/amine/Lewis acid) of 1:4:2, the desired benzimidazole **9a** was formed in 86% yield (Table 1, entry 3 vs 1). Conversely, when X = S or NMe, $AlMe_3$ gave better results, and when the reagents were combined in a ratio of 1:4:4 (ester/amino substrate/Lewis acid), the desired *N*-methyl benzimidazole **9b** (X = NMe) and benzylthiazole **9d** (X = S) products were formed in 89% and 62% yield, respectively (Table 1, entries 5 and 11). Despite numerous attempts, when 2-aminophenol (X = O) was used in the reaction, only the corresponding amide **8c** was isolated. However, we note that these amides **8c** could be subsequently converted into the corresponding benzoxazole **9d** (X = O) by *p*-toluenesulfonic acid-catalyzed azeotropic removal of water from boiling toluene (data not shown).[14]

With these results in hand, the next series of experiments involved the conversion of a hydroxymethyl *J*anda*J*el-bound benzoate ester **6** into the corresponding cleavage products **8** and **9** (Scheme 1, Table 2). In a similar fashion to the solution-phase study, 1,2-phenylenediamine **7** (X = NH) gave the best yield of product **9a** when used in conjunction with Et_2AlCl at an amino substrate/Lewis acid ratio of 2:1 (entries 1 and 2). In addition, increasing the excess of this amino substrate/Lewis acid complex over the polymer-bound ester **6** gave

Table 1. Solution-phase investigation of Lewis acid for the heterocycle formation reaction

Entry	Amine **7**		Lewis acid		Product	
	X	Equivalent		Equivalent	(%)	(%)
1	NH	3	$AlMe_3$	1.5	**8a** (48)	**9a** (36)
2	NH	2	$AlMe_3$	2	**8a** (0)	**9a** (60)
3	NH	4	Et_2AlCl	2	**8a** (0)	**9a** (86)
4	NMe	8	$AlMe_3$	4	**8b** (0)	**9b** (68)
5	NMe	4	$AlMe_3$	4	**8b** (0)	**9b** (89)
6	NMe	4	Et_2AlCl	4	**8b** (0)	**9b** (72)
7	NMe	8	Et_2AlCl	4	**8b** (0)	**9b** (85)
8	O	5	$AlMe_3$	5	**8c** (99)	**9c** (0)
9	O	4	$AlMe_3$	2	**8c** (34)	**9c** (0)
10	O	5	Et_2AlCl	4	**8c** (86)	**9c** (0)
11	S	4	$AlMe_3$	4	**8d** (0)	**9d** (62)
12	S	4	Et_2AlCl	4	**8d** (0)	**9d** (29)
13	S	7	$AlCl_3$	6	**8d** (0)	**9d** (0)

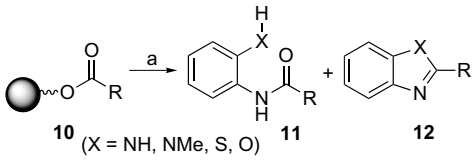
Table 2. Solid-phase synthesis of benzimidazoles, benzothiazoles and hydroxylamides from polymer-bound ester **6**

Entry	Amine		Lewis acid		Product	
	X	Equivalent		Equivalent	(%)[a]	(%)[a]
1	NH	4	Et_2AlCl	2	**8a** (0)	**9a** (77)
2	NH	8	Et_2AlCl	4	**8a** (0)	**9a** (99)
3	NMe	4	$AlMe_3$	4	**8b** (0)	**9b** (93)
4	NMe	4	Et_2AlCl	4	**8b** (0)	**9b** (86)
5	O	5	Et_2AlCl	4	**8c** (23)	**9c** (0)
6	O	10	Et_2AlCl	8	**8c** (47)	**9c** (8)
7	O	8	$AlMe_3$	4	**8c** (33)	**9c** (0)
8	O	4	$AlMe_3$	4	**8c** (50)	**9c** (0)
9	S	4	$AlMe_3$	4	**8d** (0)	**9d** (50)
10	S	8	$AlMe_3$	4	**8d** (0)	**9d** (50)
11	S	8	Et_2AlCl	4	**8d** (0)	**9d** (17)

[a] Yield of pure product based upon initial hydroxyl loading of resin used to prepare **6**.

improved yields (Table 2, entry 2 vs 1) whereby the desired product **9a** was isolated from the resin in nearly quantitative yield after purification by preparative TLC (based upon initial loading of hydroxymethyl *J*anda*J*el as estimated by DMT titration).[15] The cases where X = NMe and S also mirrored the results observed in the solution-phase model study whereby the polymer-bound ester **6** was treated with a four-fold excess of a 1:1 mixture of the amino substrate/Lewis acid ($AlMe_3$) complex, the corresponding *N*-methyl benzimidazole **9b** (X = NMe) and benzothiazole **9d** (X = S) products were obtained in 93% and 50% yields, respectively, after purification by preparative TLC (Table 2, entries 3 and 9). We also note that the direct conversion of the polymer-bound esters **6** into the desired benzoxazole products **9c** (X = O) was not feasible; by using a large excess of reagent mixture, we were able to isolate the benzoxazole **9c** in only 8% yield, (Table 2, entry 6); however, the major products from all reactions performed using the 2-aminophenol **7** (X = O) were the hydroxyl amides **8c**.

In our earlier work preparing amide cleavage products using this Lewis acid-promoted amidation chemistry, mixed bed ion-exchange resins were utilized to sequester excessively used amine reagents from the reaction mixture to yield essentially pure cleavage products. However, the use of ion exchange resins to purify the above heterocycle cleavage products gave unreliable results and often the heterocyclic products **9** were isolated in poor yields. In these cases we assume the cleaved products were retained by the ion-exchange resin along with the excessively used amine reagents and we attributed this to the slightly basic nature of the cleavage products **9**. Because of these drawbacks, after reaction had been allowed to proceed for the appropriate time, the reagents were quenched with aqueous sodium bicarbonate and the mixture was then filtered through Celite® to provide a mixture of both the cleavage products **8** or **9** and the unreacted amines **7**, which required separation by chromatography. Although this methodology provides cleavage products that are contaminated with unreacted reagents, we feel that given the many recent developments for the high throughput purification of libraries using automated, preparative-HPLC[16] that the preparation of larger libraries of benzothiazoles and benzimidazoles is a viable option. The final aspect of our study was to establish the effect of different ester groups upon the outcome of the reaction. In this case, a series of diverse polymer-bound esters **10** were prepared by reaction of an acid chloride with the hydroxymethyl *J*anda*J*el resin (data not shown). Ten different R groups were selected to include electron-rich and electron-deficient aryls, pyridyls and straight chained or bulky alkyls to examine the general applicability of this protocol. Each polymer-bound ester **10** was reacted with the series of amines **7** (X = NH, NMe, S, O) to provide the small pilot library of benzimidazoles (X = NH, NMe), benzothiazoles (X = S) **12** and hydroxyl amides (X = O) **11** (Scheme 2, Table 3).



Scheme 2. Reagents and conditions: (a) A: **7** (X = NH) (8 equiv), Et_2AlCl (4 equiv), toluene, reflux, 24 h. B: 7 (X = NMe, S, O) (4 equiv), $AlMe_3$ (4 equiv), toluene, reflux, 24 h.

As can be seen from Table 3, most of the desired products were obtained in modest to good yields. From

Table 3. Solid-phase synthesis of an array of benzimidazoles **12**, benzothiazoles **12** and hydroxyl amides **11**

Entry	X	R	Cond.[a]	Yield[b]		Entry	X	R	Cond.[a]	Yield[b]	
				11	**12**					**11**	**12**
1	NH	4-MeOPh	A	—	42	21	NMe	4-MeOPh	B	—	63
2	NH	4-MePh	A	—	63	22	NMe	4-MePh	B	—	63
3	NH	*n*-Pentyl	A	—	99	23	NMe	*n*-Pentyl	B	—	58
4	NH	4-CF_3–Ph	A	—	33	24	NMe	4-CF_3–Ph	B	—	99
5	NH	Cyclohexyl	A	58	—	25	NMe	Cyclohexyl	B	28	71
6	NH	Benzyl	A	—	42	26	NMe	Benzyl	B	—	83
7	NH	Styryl	A	—	58	27	NMe	Styryl	B	—	71
8	NH	4-Pyridyl	A	—	98	28	NMe	4-Pyridyl	B	—	83
9	NH	3-Pyridyl	A	—	71	29	NMe	3-Pyridyl	B	—	75
10	NH	2-Pyridyl	A	—	21	30	NMe	2-Pyridyl	B	—	31
11	S	4-MeOPh	B	—	46	31	O	4-MeOPh	B	50	—
12	S	4-MePh	B	—	—	32	O	4-MePh	B	37	—
13	S	*n*-Pentyl	B	—	71	33	O	*n*-Pentyl	B	75	—
14	S	4-CF_3–Ph	B	—	71	34	O	4-CF_3–Ph	B	58	—
15	S	Cyclohexyl	B	—	54	35	O	Cyclohexyl	B	42	—
16	S	Benzyl	B	—	63	36	O	Benzyl	B	58	—
17	S	Styryl	B	—	50	37	O	Styryl	B	—	—
18	S	4-Pyridyl	B	—	75	38	O	4-Pyridyl	B	42	—
19	S	3-Pyridyl	B	—	75	39	O	3-Pyridyl	B	67	—
20	S	2-Pyridyl	B	—	46	40	O	2-Pyridyl	B	46	—

[a] A: **7** (X = NH) (8 equiv), Et_2AlCl (4 equiv), toluene, reflux, 24 h. B: 7 (X = NMe, S, O) (4 equiv), $AlMe_3$ (4 equiv), toluene, reflux, 24 h.
[b] Yield based upon original hydroxyl loading of resin used to prepare **10**.

these results, it is apparent that the nature of the R group of **10** does not have a dramatic effect on the outcome of the yield of the cleavage products **11** or **12**. When R = aryl, few differences between the yields of cleavage products were observed when R = electron-rich versus electron-deficient aryl groups and good yields were also observed when R = alkyl. However, when R = cyclohexyl less satisfactory results were observed. In these cases (entries 5 and 25), the intermediate amino amide product **11** was isolated as either sole product or as a mixture with the desired product **12**. This result was attributed to the steric bulk of the cyclohexyl group.

2. Conclusion

In summary, the chemistry developed herein constitutes a simple and robust method for the conversion of polymer-bound esters into the corresponding benzimidazole and benzothiazole cleavage products by reaction with 1,2-phenylenediamines and 2-aminothiophenols in the presence of a Lewis acid. In the cases where 2-aminophenols were employed, the amidation products were obtained rather than the desired benzoxazoles. Further investigations of novel cleavage strategies are currently being performed in our laboratories and will be reported in due course.

3. Supplementary data

General experimental procedures and full characterization of all compounds is included. The Supplementary data is available online with the paper on ScienceDirect.

Acknowledgements

We gratefully acknowledge financial support from The Scripps Research Institute, The Skaggs Institute for Chemical Biology and Novartis Pharma AG Switzerland.

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13. Representative procedure: A solution of trimethylaluminum chloride in toluene (2.0 M, 600 μL, 1.2 mmol) was added to a stirred solution of *N*-methyl-1,2-phenylenediamine (147 mg, 1.2 mmol) **7** (X = NMe) in toluene (2 mL) cooled to 0 °C under an atmosphere of argon. After stirring for 10 min, the resulting solution was allowed to warm up to room temperature and stirred additional 1 h during, which time a fine white suspension had formed. This suspension was then added to a suspension of resin-bound benzoyl ester **6** (250 mg, 0.3 mmol) in toluene (3 mL) and the resulting mixture was heated to reflux for 24 h. After cooling to room temperature, a saturated aqueous solution of $NaHCO_3$ (1 mL) was slowly added and the mixture was stirred for further 10 min, filtered through a pad of Celite® and concentrated under reduced pressure. The crude product was then purified by chromatography (gradient elution, 50% toluene/ethyl acetate to 75% toluene ethyl acetate) to give *N*-methyl-2-phenylbenzimidazole **9** (58.9 mg, 93%) as a white solid.
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