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Reductive debromination of 1,2-dibromides with anisidines

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ABSTRACT

vic-Dibromides containing the α-bromocarbonyl or α-bromoaromatic moieties were reductively debrominated to furnish alkenes in high yields. *o*- and *m*-anisidines but not *p*-anisidine were found to be effective debrominating agents. The reductive debrominations were found to be *trans*-stereospecific.

Introduction

Reductive debromination of 1,2-dibromides is an important synthetic transformation in organic chemistry, and a number of methods have previously been reported, with Zn[1] being the traditional reducing agent, also with Na in liquid ammonia,[2] and a variety of other metals, (Mg,[3] Sm,[4] In[5], Ni[6]), sodium naphthalene radical anion,[7] Cr(II) salts,[8] and $FeCl_3$/In.[9] In the course of our studies toward developing an efficient synthesis of orotic acid, we uncovered an unusual stereoselective 1,2-debromination method without the use of metals, and herein we disclose our results from this study.

Results and discussion

We recently developed an efficient synthetic method for N1-substituted orotic acids.[10] The method starts with the reaction of an amine (e.g., aniline, benzyl amine, or cyclohexyl amine) with a mixture of *cis*- and *trans*-2,3-dibromosuccinimide (**1**) in THF at room temperature to yield 2-arylaminoaminomaleimide (**2**) via a tandem dehydrobromination-conjugate addition–elimination mechanism, as shown in Scheme 1.

However, when *o*-anisidine (**3**) was used, the reaction followed a different course yielding 2-aminosuccinimide **5** instead of the expected 2-aminomaleimide as shown in Scheme 2. This result suggested that in the latter case a 1,2-debromination must have taken place producing maleimide **4** first, followed by conjugate attack by the base leading to **5**. The fact that *o*-anisidine (**3**) indeed gave **5** as the major product when reacted with authentic **4** was in support of our hypothesis (Scheme 2).

We decided to explore the scope and limitations of this unusual 1,2-debromination reaction and developed it into a convenient synthetic method for converting *vic*-dibromides into *trans*-alkenes.

Reactions of *o*-anisidine with different *vic*-dibromides were examined. As expected, debromination was observed with ethyl 2,3-dibromopropionate (**6**). The resulting acrylate **7** also reacted with the amine to produce the 3-arylaminopropionate in the same manner as discussed above for maleimide **4**. In both reactions the products were α,β-unsaturated carbonyl compounds formed from 2,3-dibromocarbonyl compounds.

Reactants with the bromine atom at the benzylic position were subsequently examined. When *meso*-1,2-dibromo-1,2-diphenylethane (**8**) was reacted in refluxing THF with *o*-anisidine, *trans*-stilbene (**9**) was isolated in excellent yield (Table 1), even though the starting material did not initially dissolve well in THF. Using DMF as the reaction solvent at 80 °C showed no difference in reaction rate and yields. The formation of *cis*-stilbene was not observed.

The debromination reaction of **8** was further examined with *m*- and *p*-anisidines. *m*-Anisidine was found to be very effective and the reaction was somewhat more facile than with *o*-anisidine. However, reaction with *p*-anisidine did not yield any product.

We have further tested the debromination reaction of more *vic*-dibromides with *m*-anisidine as the debrominating agent in THF. The results are summarized in Table 1. As expected, dibromides containing the α-bromocarbonyl or α-bromoaromatic moieties were reactive and 1,2-debromination occurred smoothly in high yields. The reaction of dibromoindane **12** did not go to completion

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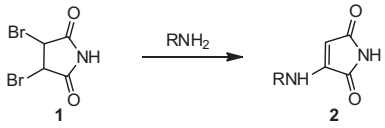
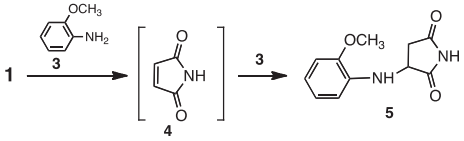


Scheme 1.

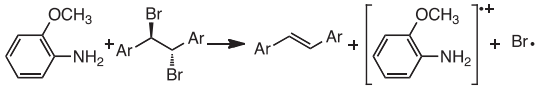


Scheme 2.

in THF, but the reaction went smoothly in DMF. In cases where both *cis*- or *trans*-alkenes are possible, only the *trans*-alkenes were obtained. Unactivated *vic*-dibromides such as *trans*-1,2-dibromocyclohexane (**14**) did not react.

The mechanism for the reductive 1,2-debromination has not been elucidated at this time. However, it is quite likely that easily oxidizable aromatic compounds of the type *o*- and *m*-anisidine transfer an electron to the bromide. It has been reported that *o*- and *m*-anisidines are more readily oxidized than *p*-anisidine.[12] The *anti*-stereospecificity can be traced to a concerted reductive elimination. Consistent with the postulated mechanism is the fact that adding one equivalent of 2,6-di-*tert*-butylphenol or TEMPO, radical scavengers, had no effect on the reaction.

We postulate that along with the *o*- or *m*-anisidine radical cation, a Br atom is formed since the secondary products derived from the anisidines had Br ring substitution (as shown in Scheme 3). A mechanistic study centered on a careful analysis and structure elucidation of secondary products from these reactions is underway and will be reported in due course.



Scheme 3.

Conclusion

In conclusion, we have uncovered an unusual and useful method for *trans*-stereospecific debromination of *vic*-dibromides that avoids the use of metals and drastic conditions and should nicely complement the existing methodologies in this area.

Acknowledgments

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References and notes

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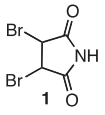
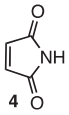
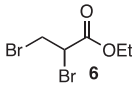
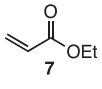
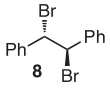
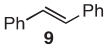
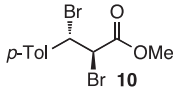
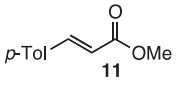
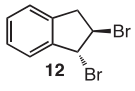
Table 1
Reductive debromination of *vic*-dibromides by anisidines[11]

Entry	Substrate	Product	Solvent	Temperature	Time (h)	Yield (isolated) (%)
1			THF	rt	2 (*o*-anisidine)	ND[a]
2			THF	rt	24 (*o*-anisidine)	ND[b]
3			THF THF THF DMF DMF	66 66 66 80 80	72 (*o*-anisidine) 24 (*o*-anisidine) 24 (*m*-anisidine) 48 (*o*-anisidine) 24 (*m*-anisidine)	92 65 79 89 78
4			THF	66	24 (*m*-anisidine)	71
5			THF DMF	66 80	48 (*m*-anisidine) 48 (*m*-anisidine)	90[c] 85
6			THF	66	48 (*m*-anisidine)	No reaction

[a] Yield not determined due to conjugate addition of amine to product.
[b] Yield not determined due to conjugate addition of amine and partial polymerization of product.
[c] Based on 51% conversion.

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11. *Experimental details:* All reagents were obtained from commercial sources and used without further purification. Typical experimental procedures are described below using meso-1,2-dibromo-1,2-diphenylethane as an example. *o*-Anisidine (123 mg, 1.0 mmol) was added to a mixture of meso-1,2-dibromo-1,2-diphenylethane ((340 mg, 1.0 mmol) in 4 mL THF. The heterogeneous mixture was refluxed for 72 hours and a homogeneous solution was obtained. The reaction was acidified and extracted with hexanes three times. The combined organic layer was dried with sodium sulfate and concentrated to give a yellow solid as crude product, which was purified by column chromatography to give *trans*-stilbene (165 mg, 92%) as a white crystal. The ^{1}H NMR spectrum was identical with that found in the Aldrich library.
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