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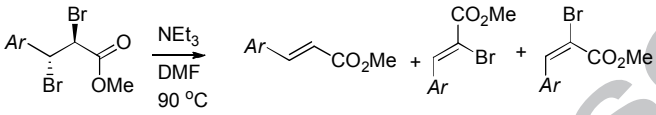

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Competitive, substrate-dependent reductive debromination/dehydrobromination of 1,2-dibromides with triethylamine

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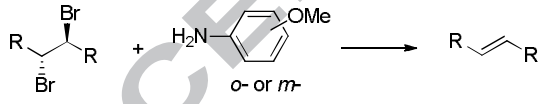
ABSTRACT

The interaction of various 1,2-dibromides with NEt_3 under various conditions (THF and DMF, respectively) at different temperatures was investigated. Our results from these reactions show that substrate dependent dehydrobrominations compete with reductive debrominations. A comprehensive discussion of these competitive pathways is offered.

1. Introduction

We recently uncovered a new reductive debromination of vicinal dibromides derived from either α,β-unsaturated carbonyl compounds, or aryl substituted alkenes (e.g., stilbene, indene) using *o*- or *m*-anisidine in a *trans*-stereoselective manner.[1] We postulated that these easily oxidizable aromatic compounds affect the elimination via electron transfer to the dibromide, with concomitant double bond formation in a concerted fashion (Scheme 1).



Scheme 1. Reductive debromination with *o*- or *m*-anisidine

We rationalized the *anti*-stereospecifity of the reductive elimination by invoking a concerted mechanism via a one-electron transfer to the bromine atom. We were curious as to whether the use of triethylamine (NEt_3) instead of the easily oxidizable arenes *o*- and *m*-anisidines would also result in reductive elimination or E2 and/or E1cB reactions with aryl or carboxyl substituted *vic*-dibromides. In addition, we included "activated" 1,2-dibromides derived from α,β-unsaturated carboxylic acid derivatives (esters and amides, respectively) to assess the role of the adjacent carbonyl group in the mechanism of elimination or debromination. We report in this *Letter* our results from this study. Our findings point to a substrate-dependent competition between reductive debrominations and dehydrobrominations.

2. Results and Discussion

The 1,2-dibromides used in this study were prepared from the corresponding alkenes by bromine addition and purified by column chromatography on silica gel. The results from the debrominations/dehydrobrominations are presented in Table 1. Two different solvents, THF and DMF were used for most reactions with similar results except for entries 3 and 5. To our surprise, *meso*-stilbene dibromide **4** (entry 1) underwent exclusively reductive debromination with NEt_3, mimicking the reaction with the *o*- or *m*-anisidines. The dibromide **6**, derived from ethyl acrylate, on the other hand, suffered regioselective dehydrobromination under much milder conditions (~20 °C) in THF to give **7**, presumably by an E1cB mechanism. The mildness of the elimination conditions can be traced to the increased acidity of the α-H in **6**. Placement of an aryl group (*p*-tolyl) at the β-carbon, as in **8**, likewise resulted in dehydrobromination leading to the isomeric vinyl bromides **9** and **10** in refluxing THF; however, switching to DMF and raising the temperature to 90 °C also gave significant amounts of the reductive debromination product **11** in addition to **9** and **10** in similar proportions. The corresponding *N*,*N*-dimethyl amide **12** gave exclusively the reductive debromination product **13** in either

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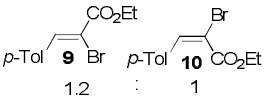
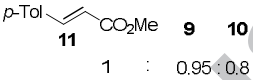
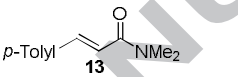
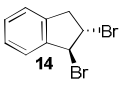
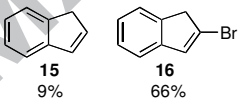
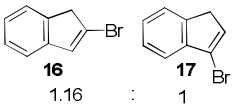
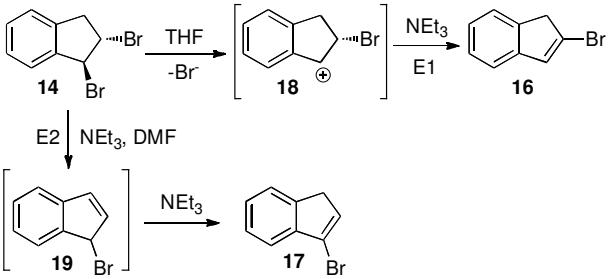
Table 1. Competitive dehydrobromination-reductive debromination of selected *trans*-1.2-dibromides with NEt_3

Entry	Substrate	Conditions	Product(s)	Yield, %[a]
1	PhCHBrCHBrPh **4**	THF, RT, 1.5h	No reaction	0
2		DMF, 90 °C, 36h	 **5**	88
3	$CH_2BrCHBrCO_2Et$ **6**	THF, RT °C, 1.5h	 **7**	92
4		DMF, RT, 1.5h	**7**	91
5	*p*-TolCHBrCHBrCO$_2$Me **8**	THF,66 °C, 36h	 **9** 1.2 : **10** 1	84
6		DMF, 90 °C, 36h	 **11** 1 : **9** 0.95 : **10** 0.8	61
7	*p*-TolCHBrCHBrCONMe$_2$ **12**	THF, 66 °C, 24h	 **13**	65
8		DMF, 90 °C, 36h	**13**	92
9	 **14**	THF, 66 °C, 24h	 **15** 9% **16** 66%	75
10		DMF, 90 °C, 24h	 **16** 1.16 : **17** 1	74

[a]Isolated yields

solvent, the reaction in DMF at higher temperature being more efficient.

The dibromide **14** derived from indene gave mixed results. The reaction of **14**[2] in THF (Entry 9) at reflux gave the debromination product indene (**15**) in only 9% yield, with the dehydrobromination pathway dominating (66%) furnishing 2-bromo-1-indene **16**[3] as the exclusive elimination product. On the other hand, reaction in DMF at 90 °C (Entry 10) furnished a nearly equimolar mixture of both possible dehydrobromination products **16** and **17**.[4] The latter two results from Entries 9 and 10 deserve immediate comment. The exclusive formation of the '2-isomer' of bromoindene, **16,** is surprising at first glance, since an E2 elimination with NEt_3 would require an *anti* arrangement of the β-proton and the α-halogen. However, due to the *trans* configuration of bromine atoms in **14** the β-proton is *cis* to the bromine atom on C2, and the proton on C1 is also *cis* to the bromine atom on C2. In fact, if an E2 type elimination is to be expected, then the more acidic proton on C1 would be abstracted preferentially, leading to **17**, rather than **16**. Since the E2 is impeded here due to stereoelectronic reasons, we postulate that the only pathway leading to **16** is an E1 elimination via a stable carbocation on C1. It is also conceivable that the *cis*-elimination to give **16** might proceed via an E1cB pathway[5] but we consider this pathway less tenable since the less acidic proton at C2 would have to be abstracted to give **16**. In Entry 10, on the other hand, in addition to the E1 component, a less favorable E2 elimination at higher temperature with the relatively weak base[6] NEt_3 is competing, initially leading to **19.** The latter undergoes a base-catalyzed double bond isomerization to **17**. Scheme 2 depicts the pathways whereby bromoindenes **16** and **17** are formed in these reactions. Stilbene dibromide **4** (Entry 1) does not undergo E2, and reductive elimination is observed only in DMF. By replacing one of the aryl groups with a carboxyl group, as in **6** and **8**, the extent of reductive debromination was minimized. In fact, ester **6** solely underwent elimination in either solvent at room temperature, presumably by an E1cB mechanism.



Scheme 2. Mechanistic pathways leading to **16** and **17**

The results from the interaction of amide **12** in THF or DMF with NEt_3 (Entry 7) were unexpected since exclusive reductive debromination was observed here and no E1cB product was isolated. This result is not entirely surprising since the amide

carboxyl group is considerably less electron-withdrawing owing to the electron-donating resonance characteristics of the amide nitrogen. The reductive debrominations observed in a few cases are not discussed further here since in our previous report on similar reactions with anisidines we had offered a reasonable mechanism for these reactions.

3. Conclusions.

After having uncovered a new reductive debromination of non-activated 1,2-dibromides with *o*- and *m*-anisidines, and in an effort to shed light on the types of interaction of vicinal dibromides with tertiary amines, we studied the corresponding reactions of 1,2-dibromides derived from non-activated arylalkenes as well their activated counterparts, α,β-unsaturated carboxyl derivatives, with NEt_3. The reactions were conducted in two different solvents (THF and DMF, respectively) at different temperatures, and based on the product distribution under the conditions applied, the outcome of the NEt_3 promoted reactions turned out to be quite different from that achieved with *o*- and *m*-anisidine, respectively. With the latter weak aromatic bases that are easily oxidizable, exclusive reductive debromination was observed in activated and non-activated 1,2-dibromides (pK_a of the conjugate acids, respectively, of *o*-anisidine 4.52, *m*-anisidine 4.23).[7] On the other hand, with a much stronger base like NEt_3 (pK_a of conjugate acid 10.75), and in particular with activated dibromides, the dehydrobromination by an E1cB dominates, except for the *N,N*-dimethyl amide **12**, where in either solvent only the reductive debromination product **13** was isolated. With the ester **8**, the reductive debromination product 11 was absent in THF at 66 °C, but its proportion relative to the E1cB products **9+10** was ca. 36%. Apparently, the reductive debromination pathway requires higher temperatures than the E1cB reaction. Thus, with the deactived dibromide **4**, the E1cB pathway is precluded, but the reductive debromination pathway still requires 90 °C in DMF. The question why the debromination dominates with the *N,N*-dimethyl amide **12** can be traced to the fact that the E1cB in this case is much less preferred due the decreased acidity of the α-hydrogen than with esters **6** or **8** (pK_a values of α-CH in ethyl acetate and *N,N*-dimethylacetamide are 25 and 30, respectively).[8]

Acknowledgments

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6. E2 Eliminations require strong bases. Triethylamine is not a common E2 base due to its relatively low basicity (pK_a of the conjugate acid 10.75) as compared to, e.g., 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a popular E2 base (pK_a of conjugate acid 12): Srivastava, R. *J. Mol. Catal A: Chem*. **2007**, *264*, 146-152.
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8. These pK_a values were taken from a Table in J. G. Smith *Organic Chemistry*, 4th ed.; McGraw-Hill: New York, 2014; p A2.

Highlights

- Reductive debrominations compete with dehydrobrominations..
- C–H acidity of the substrates determines selectivity.
- Triethylamine is not an efficient base for reductive debromination.