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Ring Expansion/Homologation-Aldehyde Condensation Cascade using *tert*-Trihalomethylcarbinols

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Abstract

Treatment of cyclic *tert*-trihalomethylcarbinols with CrCl_2 in THF/HMPA in the presence of aryl or aliphatic aldehydes initiates a cascade sequence of one carbon ring expansion-olefination affording conjugated exo-cyclic ketones. Acyclic *tert*-trihalomethylcarbinols undergo a comparable cascade of one carbon homologation-olefination.

Trihalomethylcarbinols and their derivatives are a diverse¹ and readily accessible class of functionalized alcohols.² Their reduction, *inter alia*, electrochemical,³ zero-valent metals/metal salts,⁴ or aqueous Cr(II) ,⁵ principally induces elimination to the corresponding 1,1-dihaloolefin. However, our laboratories recently observed that *sec*-trihalomethylcarbinol derivatives follow a different reaction manifold when reduced with Cr(II) salts in THF leading stereoselectively to (*Z*)- α -haloenol esters and (*Z*)- β -haloenol ethers.⁶ We consequently examined the behavior under similar conditions of *tert*-trihalomethylcarbinols in the presence of aldehydes and report herein a cascade sequence⁷ of one carbon ring expansion/homologation-olefination affording conjugated ketones.⁸

The cascade sequence was optimized using carbinol **1**⁹ ($X = \text{Cl}$) and benzaldehyde **2** as the test system. The best yield of adduct **3**¹⁰ was obtained using CrCl_2 (6 equiv) in THF/HMPA (2:1) at 40 °C (Table 1, entry 1). Using the tribromo-version of **1** ($X = \text{Br}$), the results were identical, except the reaction only required 2 h instead of the 4 h when $X = \text{Cl}$. The output of

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Supporting Information Available Synthetic procedures, analytical data, X-ray files, and ¹H/¹³C spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

3 did not improve using a lower THF/HMPA ratio (i.e., 1:1) and it decreased linearly as the ratio increased in favor of THF. Other solvents or their combinations, e.g., THF only, DMF, EtOAc, dioxane, and HMPA, were not satisfactory. There was also a strict dependence on the amount of CrCl_2 ; 5 and 4 equivalents gave **3** in 51% and 30% yield, accordingly. Efforts to use fewer equivalents of CrCl_2 by coupling the reaction to a regeneration system showed promise, but clearly need further improvement. For instance, under otherwise identical conditions as entry 1, CrCl_2 (1 equiv)/Mn powder (8 equiv) and CrCl_2 (1 equiv)/Fe powder (10 equiv) gave rise to **3** in 58% and 42% yield, respectively.

We were gratified to find that the cascade was also applicable to aliphatic (entry 2, **4** $\rightarrow$ **5**¹⁰), α,β -unsaturated (entry 3, **6** $\rightarrow$ **7**¹⁰), and electron rich (entry 4, **8** $\rightarrow$ **9**¹⁰ and entry 5, **10** $\rightarrow$ **11**¹¹) aldehydes. In all, only exo-cyclic olefins were generated including **5**, the thermodynamically less stable positional isomer. Notably, the yield of adduct, as demonstrated in the condensation of **1** with **10** (entry 5), could be ameliorated utilizing a modest excess (1.5 equiv) of carbinol. Electron deficient aldehydes were also suitable substrates, e.g., **12** $\rightarrow$ **13** (entry 6). Contrary to expectations,⁸ the ring enlargement-olefination of **14** favored **15**,¹² the product of migration of the less substituted carbon, over **16**¹³ by a 5:1 ratio (entry 7). Other ring sizes could be accommodated as well: cyclobutyl carbinol **17** evolved cyclopentenone **18**¹⁰ (entry 8) and cyclohexyl carbinol **19**^{9b} furnished cycloheptenone **20**¹⁰ (entry 9). To gain some insight into the influence of relative stereochemistry and conformation on the efficiency of the ring expansion process, the conformationally constrained *erythro*/*threo*-pairs **21/22** (entry 10) and **24/25** (entry 11) were subjected to the standard reaction conditions. The *erthyro*-isomers **21** and **24**, whose trichloromethyls are equatorially disposed, afforded significantly greater yields of the expected adducts **23** and **26**, respectively, consistent with better orbital overlap in the transition state. Simple elimination to the corresponding 1,1-dichloroolefin accounted for the majority of the remaining material balance in all of these cases. Finally, comparable homologation-olefinations could be achieved using acyclic trihalocarbinols as evident by the isolation of **28** in good overall yield from the commercial carbinol **27** (entry 12).

While the mechanistic details have not been established, at least two pathways seem plausible in light of the existing data (Scheme 1). Initial metallation of the trihalomethyl moiety generates the key dihalochromium intermediate **29**. A second round of metallation leads to **30**,⁶ which rearranges to dichromium ketone **31**. The latter may exist as the dichromium enolate **37**. Either would be expected to add rapidly to the aldehyde and collapse to the final product, **33**. Alternatively, α -elimination of **29** forms carbene **34** and hence α -haloenol **35**, its rearrangement product. Addition to the aldehyde culminates in **33** via reduction of adduct **36**. When an equimolar mixture of 2-chlorocyclohexanone and **2** was added to excess CrCl_2 in THF/HMPA (2:1), **3** was isolated in only 34% yield. This suggests the keto tautomer of **35**, i.e., **38**, does not make a significant contribution to product formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Proposed Cascade Mechanism.

Table 1

Ring Expansion/Homologation-Aldehyde Condensation Cascade^a

entry	carbinol	aldehyde	product	yield (%)
1		PhCHO 2		72
2		Ph-CH2-CHO 4		75
3		Ph-CH=CH-CHO 6		65
4				60
5				74 82 ^c
6				49
7		2		50
8		2		11
9		2		63
10		2		52
11		2		46 38
12		2		57 20
		2		70

^b Structure and relative stereochemistry confirmed by X-ray analysis of the (p-tolylsulfonyl) hydrazone.^d Structure and relative stereochemistry confirmed by X-ray analysis.^a Trihalocarbinol (1 mmol) was added to a stirring suspension of CrCl₂ (6 mmol) and aldehyde (1 mmol) in THF/HMPA (2:1, 7 mL) at 40°C for 4 h, quenched with water and purified.^c Used 1.5 equivalents of carbinol.