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Catalytic Insertion of Aldehydes into Dihalogenonitroacetophenones via Sequential Bond Scission-Aldol Reaction-Acyl Transfer

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Abstract

A catalytic process that provides dihalogenated nitro alcohols in up to 99% yield and with 100% atom economy is described. In-situ cleavage of dihalonitroacetophenones affords nitronates that undergo Lewis acid catalyzed addition to aldehydes. Final benzoylation renders the sequence irreversible and regenerates the bond scission and acyl transfer agent.

Graphical abstract

The development of synthetic methodologies for the production of organofluorines has received widespread attention in the past decade.¹ The general interest and advance in fluorination chemistry has primarily been fueled by the growing impact of fluorinated pharmaceuticals.² Surprisingly, a recent survey on the diversity of elements in small drugs revealed that chlorine is much more frequently encountered in US FDA approved pharmaceuticals than fluorine.³ Impressive examples of the total synthesis of chlorinated natural products have appeared in the literature.⁴ But the pace of introduction of new methods that furnish organochlorine compounds⁵ has fallen behind the compelling progress with organofluorine synthesis.

Aliphatic nitro compounds are versatile building blocks that provide unique opportunities for the construction of multifunctionalized carbon frameworks. This has been exemplified by nitroaldol and Michael reactions,⁶ allylations,⁷ arylations,⁸ alkylations⁹ and amide bond synthesis.¹⁰ The general popularity of nitroalkanes is in stark contrast to the scarce use of halogenated derivatives. In particular, the development of new methods that exploit

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dihalogenated nucleophiles such as dichloro- and difluoronitronates bears huge synthetic potential that remains to be explored. A persisting problem is that the generation of dichloronitromethane and its carbanion requires conditions that impede scale-up and favor side reactions including dehalogenation and carbene formation. The impracticality of the production and handling of dichloronitromethane and its conjugated base, which can be prepared from potassium nitroacetate and chlorine gas or via tin insertion into trichloronitromethane,¹¹ has limited synthetic applications. The lack of reports on C-C bond formation with difluoronitromethane, first prepared by Bissell by thermal decomposition of difluoronitroacetamide and careful isolation at very low temperatures, can be attributed to its high volatility.¹² We hypothesized that these drawbacks can be overcome with a new synthetic methodology that exploits mild *in situ* generation of dihalonitronates **2** from readily available bench-stable nitroketones **1** (Scheme 1).

The possibility of practical dichloronitronate and difluoronitronate formation under mild reaction conditions and subsequent trapping with a suitable electrophile, for example an aldehyde, would provide an unprecedented entry to the direct synthesis of a variety of dihalogenated nitro compounds. However, at least three additional issues inherent to the nitroaldol reaction would have to be addressed. First, the use of dihalonitronates, which are excellent leaving groups and expected to favor the retro-aldol reaction, would require a strategy that renders the C-C bond formation step irreversible. Second, mild reaction conditions would be needed to extend the application scope to enolizable aldehydes. Third, nitroaldol reaction protocols typically have low atom economy and almost exclusively call for large excess of nitroalkanes unless solvent free conditions are applied.¹³ Therefore, a catalytic procedure that utilizes equimolar amounts of both the substrate and the pre-nucleophile forming the nitronate is very desirable. In particular, the general requirement for 5–10 equivalents of nitromethane or other nitroalkanes, which furnish the intermediate nitronate via deprotonation in the presence of base, has been a longstanding drawback of the Henry reaction. We expected that this might be solved with a methodically different approach based on *in situ* nitronate formation via C-C cleavage of a bench-stable precursor rather than nitroalkane deprotonation. A procedure devoid of an acid-base equilibrium would also facilitate trapping of the aldol product via acylation and thus eliminate any possible retro-aldol interference. We now wish to report the development of a synthetic methodology that addresses all issues outlined above. We further discuss the synthetic scope and provide mechanistic insights into the catalytic process that involves sequential bond-scission of **1**, nucleophilic addition of **2** to aldehydes and final benzoyl group transfer to give **3** or **9** with 100% atom economy.

At the beginning of this study, we decided to evaluate the feasibility of C-C scission of dichloronitroacetophenone, **1a**, which was readily prepared in 80% yield by dichlorination of α -nitroacetophenone with *N*-chlorosuccinimide. NMR analysis confirmed the anticipated formation of benzoyl pyrrolidine, **4**, and dichloronitromethane, **5**, upon addition of stoichiometric amounts of pyrrolidine at room temperature (see ESI). The two scission products **4** and **5** were initially present in equimolar amounts and the cleavage of **1a** was almost quantitative after 75 min. The dichloronitromethane/benzoyl pyrrolidine ratio, however, decreased over time which may be attributed to decomposition of **5**. Because of the

reversibility with halogenated nitroalkanes and the common necessity to use considerable excess of nitroalkanes in the Henry reaction, we were not surprised that the reaction between **5** and 4-nitrobenzaldehyde, **6a**, was sluggish even in the presence of additional base and Lewis acids. By contrast, the reaction course outlined in Scheme 1, i.e. the cleavage of **1a** and subsequent addition of the dichloronitronate **2a** and the benzoyl moiety to **6a** was achieved when we employed 3 equivalents of LiBr and stoichiometric amounts of Et₃N or DMAP in THF. The replacement of pyrrolidine with triethylamine or DMAP circumvents the generation of free **5** and sets the stage for irreversible C-C bond formation. Under these conditions, we were able to isolate 2,2-dichloro-2-nitro-1-(4-nitrophenyl)ethyl benzoate, **3a**, in up to 74% yield (ESI), and we obtained crystallographic proof for the proposed 3-step reaction sequence (scission of **1a**, C-C bond formation, acyl transfer) with two aldehyde substrates (Scheme 1).¹⁴

Further reaction analysis suggested that a catalytic version of this transformation should be possible. At this point, we decided to restrict our development efforts to conditions that utilize readily available, inexpensive catalysts and equimolar amounts of **1a** and aldehyde to afford a practical method with high atom economy. Comprehensive screening efforts showed that the formal insertion of **6a** into **1a** occurs quantitatively when catalytic amounts of LiBr and (*i*-Pr)₂N⁺Et are used in THF (ESI). We also observed almost 100% conversion and no sign of side reactions with other aldehydes when homogeneous conditions were maintained, and we therefore based the solvent selection on the substrate solubility (ESI). With an optimized method in hand, we then investigated the substrate scope. As shown in Table 1, the reaction between **1a** and aromatic substrates exhibiting several functional groups gave excellent results, ranging from 88% to 99% yield (entries 1–8). Similarly, the heterocyclic aldehydes **6i** and **6j** were smoothly converted to the dichloronitro benzoates **3i** and **3j**, however, the yield decreases when electron-donating groups are present (entries 9–11). The mild conditions tolerate enolizable substrates, and the insertion of hydrocinnamaldehyde, **6l**, and hexanal, **6m**, into **1a** gave the dichloronitro benzoates **3l** and **3m** in very good yields (entries 12 and 13).

To highlight the utility of the dihalonitromethyl derived alcohols **3**, we employed a procedure reported by Ballini to affect denitration and extension of the carbon bond framework (Scheme 2).¹⁵ We were pleased to find that the AIBN initiated radical allylation and reduction occurred with typical literature yields. The reduction of **3e** with tributyltin hydride furnished **7** in 76% yield and the reaction with allyltributylstannane gave **8** in 70% yield. The formation of **7** shows that this work provides practical access to compounds having a dichloromethyl group which is an important subunit in pharmaceuticals including Mitotane, Chloramphenicol, Trichlormethiazide and Methoxyflurane.^{16,17} The allylation of **3e** toward **8** exemplifies that the terminal nitrodichloromethyl moiety in **3** provides an entry to the synthesis of elongated structures with a central dichloromethylene group.

The success with the catalysis summarized in Table 1 led us to question if this method can be extended to difluoronitroacetophenone, **1b**. After several attempts, we were able to prepare **1b** by fluorination of α -nitroacetophenone with Selectfluor in 75% yield (ESI). Following the protocol used for the coupling of aldehydes and **1a** we obtained the corresponding difluoronitromethyl derived alcohols **9a–e** in 88 to 99% yield (Scheme 3).¹⁸

Finally, we investigated the mechanism of the formal aldehyde insertion into dihalonitroacetophenones. The cleavage of dichloronitroacetophenone in the presence of catalytic amounts of diisopropylethylamine and lithium bromide and the subsequent reaction with 4-nitrobenzaldehyde to the *O*-benzoyl nitroaldol product were monitored by React FTIR analysis (Figure 1). A THF solution of 4-nitrobenzaldehyde, **6a**, and lithium bromide (20 mol%) was stirred under nitrogen atmosphere at room temperature showing the characteristic carbonyl stretching absorption of the aldehyde group at 1710 cm⁻¹. After 10 minutes, one equivalent of **1a** was added. The ketone **1a** has strong IR absorptions at 1720 and 1705 cm⁻¹ that essentially overlap with the aldehyde stretching. After another 3 minutes, diisopropylethylamine (20 mol%) was added to start the reaction. Immediately, a steady decrease in the combined aldehyde and ketone stretching absorptions at 1712 cm⁻¹ was observed while a new signal at 1746 cm⁻¹ appeared. The latter signal correlates well to the IR absorption of the isolated benzoyl ester at 1741 cm⁻¹ and was therefore assigned to the reaction product **3a**. The conversion of **6a** was almost complete after 5 h. The cleavage of **1a** with a tertiary amine was also investigated by ¹H and ¹³C NMR spectroscopy (see ESI). Mixing of **1a** and triethylamine did not show any spectroscopic change even after 20 minutes, indicating that the equilibrium of the C-C bond scission lies far on the side of the starting materials. However, this mixture showed spontaneous and quantitative cleavage of **1a** and formation of methyl benzoate and dichloronitronate upon addition of methanol. This suggests that the tertiary amine generates small amounts of the free dichloronitronate which is sufficient to initiate the reaction sequence. We found no sign of a reaction between dichloronitroacetophenone and methanol in the absence of triethylamine. The tertiary amine, or another nucleophile such as DMAP, is therefore essential for (a) the C-C scission of the dihalonitroacetophenone which generates the dihalonitronate and (b) the transfer of the benzoyl group to the intermediate aldol product.

Based on our NMR and IR studies, we propose the catalytic cycle shown in Scheme 4. The initial nucleophilic attack of (*i*-Pr)₂NEt at the dihalonitroacetophenone, **1**, which might be activated by the Li Lewis acid, generates small amounts of dihalonitronate **2** and the benzoylammonium species **A**. The lithium catalyzed aldol reaction with the aldehyde may involve a chairlike transition state **B** and yields **C** which is consumed by irreversible benzoylation with **A**. The formation of **3** coincides with the regeneration of (*i*-Pr)₂NEt and LiBr. In accordance with our mechanistic studies we found that the reaction does not occur in the presence of LiBr unless a *N*-nucleophile is added which rules out the involvement of an acyl bromide intermediate. Altogether, the formal insertion of an aldehyde into **1** involves 3 sequential steps controlled by a tertiary amine or another nucleophile and a Lewis acid. The latter activates the aldehyde and catalyzes the central C-C bond forming step and the former induces the scission of **1** and acts as an acyl transfer agent to capture the final product.¹⁹

In summary, we have introduced a catalytic method that inserts aldehydes into dihalonitroacetophenones providing unprecedented access to a series of α,α -dihalogenated nitro alcohols with excellent yields. Mechanistic studies demonstrate that this process is based on sequential C-C cleavage, nucleophilic addition and acyl transfer steps. The initial dihalonitroacetophenone scission generates a dihalonitronate that undergoes Lewis acid

catalyzed addition to an aldehyde substrate which is finally benzoylated. While the central C-C bond formation is catalyzed by lithium bromide, the roles of diisopropylethylamine are to cleave the dihalonitroacetophenone and to act as acyl transfer agent. This method has several attractive features: The reaction is irreversible and involves *in situ* formation of reactive dihalonitronates under mild conditions (1), elevated temperatures and expensive transition metal complexes are avoided (2), and the use of stoichiometric amounts of the substrate and reagent affords 100% atom economy (3). Altogether, this methodology effectively circumvents the common deprotonation step in traditional aldol chemistry to generate a nucleophile. We believe that the combination of bond scission with mild *in situ* generation of a reactive intermediate described herein holds considerable promise for the introduction of currently elusive nucleophiles and the development of other reactions that are currently restricted by interfering acid/base equilibria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. React FTIR analysis of the C-C scission/nitronate addition/benzoyl transfer sequence using **6a** as substrate in THF. The arrows indicate the addition of dichloronitroacetophenone (BDCNM) and (*i*-Pr)₂NEt.

Catalytic bond scission and formal aldehyde insertion with a readily available dihalonitronate precursor

Scheme 1.

Features of the LiBr/amine catalyzed C-C scission/nitronate addition/benzoyl transfer sequence and crystallographic analysis of the 2-nitro- and 4-nitrobenzaldehyde insertion products.

Scheme 2.
Denitration and allylation of **3e**.

Scheme 3.

Synthesis of *O*-benzoyl α,α -difluoro- α -nitro alcohols **9** using **1b**.

Scheme 4.
Proposed mechanism of the catalytic C-C scission-nitronate addition-benzoyl transfer sequence.

Table 1Synthesis of *O*-benzoyl α,α -dichloro- α -nitro alcohols^a

Entry	Aldehyde	Product	Yield (%) ^b
1 ^c			90
2 ^d			94
3 ^e			98
4 ^f			99
5 ^c			96

Entry	Aldehyde	Product	Yield (%) ^b
6 ^f	 6f	 3f	99
7 ^d	 6g	 3g	95
8	 6h	 3h	88
9 ^f	 6i	 3i	99
10 ^f	 6j	 3j	91

Entry	Aldehyde	Product	Yield (%) ^b
11	<p>6k</p>	<p>3k</p>	59
12 ^{f,g}	<p>6l</p>	<p>3l</p>	93
13 ^{f,g}	<p>6m</p>	<p>3m</p>	81

^aReaction conditions: LiBr (0.05 mmol), DIPEA (0.05 mmol), aldehyde **6** (0.25 mmol) and **1a** (0.30 mmol) in 0.15 mL of anhydrous ether at 25 °C.

^bIsolated yields.

^cTHF.

^d(*i*-Pr)₂O.

^eEt₂O.

^fMTBE.

^gThe aldehyde was added in portions.