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Unusual Reactivity of Nitronates with an Aryl Alkyl Carbonate: Synthesis of α-Amino Esters

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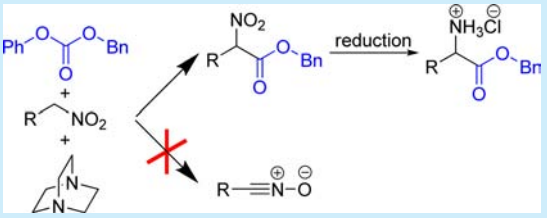
Supporting Information

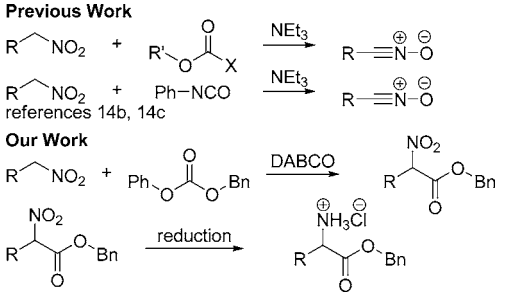
ABSTRACT: The monoanions of nitroalkanes are ambident nucleophiles that react with carbonate electrophiles through the oxygen atom. Products arising from reactivity at the carbon atom will yield α-nitro esters, which are precursors for α-amino esters. We demonstrate this in the reactions of nitroalkanes with benzyl phenyl carbonate and DABCO where α-nitro esters are obtained instead of nitrile oxides. The products are readily reduced to α-amino esters. This pathway could be a safe alternative to the Strecker reaction.



Proteinogenic and non-proteinogenic α-amino acids have found utility in various fields such as catalysis,[1] medicinal chemistry,[2] and materials science.[3] Among the various methods for the synthesis of α-amino acids,[4] the Strecker reaction[5] has one of the broadest substrate scopes. In this reaction, an imine (electrophile) is treated with cyanide (nucleophile) to obtain α-amino nitriles. The cyanide moiety is hydrolyzed to yield the carboxyl group of the amino acid. A major drawback of this approach is the toxicity of cyanide. This has led to alternative approaches wherein cyanide is generated in situ.[6] In order to completely avoid the use of cyanide, several groups have looked at alternative one-carbon synthons.[7,8] Among these, carbon dioxide is a convenient one-carbon synthon.[9] However, mostly high pressures of CO_2 are required, and the substrate scope is limited.[10,11]

In this context, the synthesis of α-nitro esters represents a convenient and easily scalable alternative to the Strecker reaction.[12] The Seebach group has shown that dialkyl carbonates can react with dianions of nitroalkanes to give α-nitro esters.[12j,k] The nitro esters can be readily reduced to give α-amino esters.[13] Formation of dianion is required to force reactivity through the carbon atom of the ambident nitronate anion. Indeed, the monoanion preferentially reacts through the oxygen atom with electrophiles such as choloroformates, carbonates, and isocyanates to yield nitrile oxides.[14] The dianions are generated by using 2 equiv of a strong base at low temperatures. Additionally, in certain cases like β-phenyl nitroethane the second deprotonation is not regioselective.[12j−l] As a result, inseparable mixtures of the product nitroesters are obtained. The above limitations can be overcome if the reaction can be carried with the monoanion of nitroalkanes. This would then represent a safe and scalable alternative to the Strecker reaction. Herein, we detail an approach where we overturn the preferred reactivity pattern of nitronate anions by using a nucleophile. In the process, we generate α-nitro esters under mildly basic conditions. The nitro group can be reduced readily to obtain the corresponding α-amino esters in good yields (Scheme 1). This provides an operationally simple alternative to the use of toxic cyanide for the synthesis of α-amino acids.

Scheme 1. Synthesis of α-Amino Esters Using Carbonates



Our initial studies were guided by the proposed mechanism shown in Scheme 2. We began our studies with benzyl phenyl carbonate as our one-carbon synthon. In this carbonate, the phenoxy moiety is a good leaving group that can be selectively expelled upon attack of a nucleophile. The benzyloxy moiety cannot be expelled in this manner, and this ensures that the carbonyl group in the product will not be susceptible to nucleophilic attack. We posited that nucleophilic activation of benzyl phenyl carbonate by 1,4-diazabicylco[2.2.2]octane (DABCO) would result in the generation of a phenoxide anion. Phenol, the conjugate acid of this anion, has a higher pK_a than nitroalkanes (Scheme 2).[15] Therefore, the phenoxide anion will deprotonate a nitroalkane to generate a nitronate anion. The monoanion can then react with the activated carbonate either through the oxygen atom or through the carbon atom. Reaction through the oxygen atom would result in the formation of a nitrono carbonate. However, attack of

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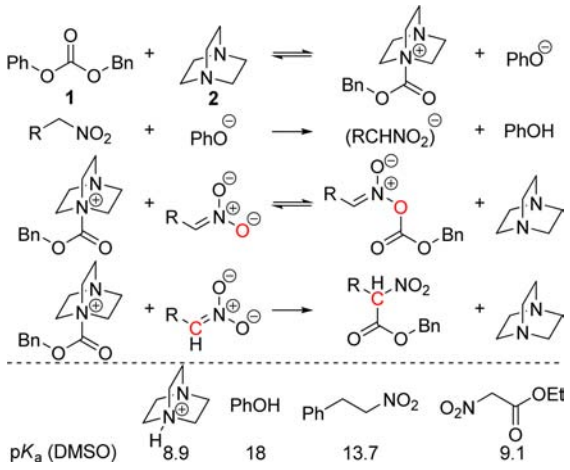
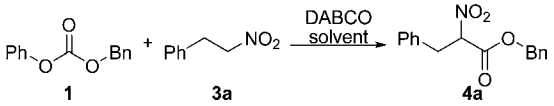
Scheme 2. Initial Mechanistic Hypothesis



DABCO on the nitronocarbonate was expected to regenerate the nitronate anion. On the other hand, reaction through the carbon atom would lead to formation of an α-nitro ester. The carbonyl group in this compound is unlikely to be attacked by DABCO due to its lower electrophilicity. On the basis of pK_a values, DABCO is expected to deprotonate the product (confirmed by ^{1}H NMR studies, vide infra). This should ensure that reaction through the carbon atom is irreversible.

To test the feasibility of this approach, a mixture of 2-phenylnitroethane, benzyl phenyl carbonate, and DABCO was refluxed in THF for 20 h. We obtained the α-nitro ester in 49% yield after chromatographic purification (Table 1, entry 1). ^{1}H

Table 1. Solvent Screen[a]



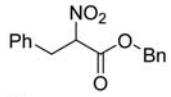
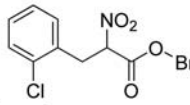
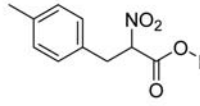
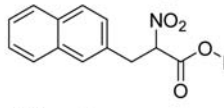
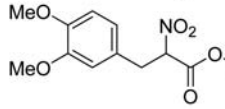
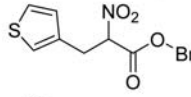
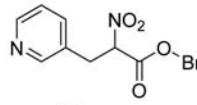
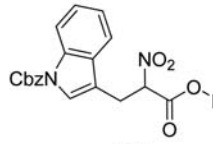
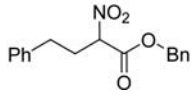
entry	solvent	temp (°C)	time (h)	% yield[b]
1	tetrahydrofuran	66	20	49
2	acetonitrile	50	64	58
3	ethyl acetate	60	59	64
4	isopropyl acetate	60	67	59
5	chlorobenzene	50	64	58
6	DMSO[c]	70	2.5	52
7	neat[d]	60	12	76
8	DMSO[d,e]	60	5	77

[a]Conditions: carbonate (2.0 equiv), DABCO (4.0 equiv), ~ 0.66 M of **3a**. [b]Yield of product after column chromatography. [c]~0.33 M of **3a**. [d]Carbonate (3.0 equiv), DABCO (2.0 equiv). [e]DMSO (3.0 equiv).

NMR studies indicated that DABCO does not deprotonate the nitroalkanes (see Supporting Information). When benzyl *p*-nitrophenyl carbonate and benzyl pentafluorophenyl carbonate were used, the nitroalkane remained unreacted. This is possibly due to the lower basicity of the corresponding phenoxides. Using this as our standard reaction, we set out to identify the most suitable nucleophile. We performed reactions with various nucleophiles, and the percent conversion of 2-phenylnitroethane was monitored by gas chromatography (GC) using an internal standard. While pyridine, DMAP, and imidazole appeared to be competent nucleophiles, DABCO gave the highest conversions (see Supporting Information). We then attempted optimization of the solvent system using the same substrates (Table 1). One of the highest yields was obtained when the reaction was performed under solvent-free conditions (entry 7, Table 1). From the initially hypothesized mechanism, it appeared that addition of a small amount of DMSO might speed up the reaction as it is known to stabilize cations. Indeed, addition of 3 equiv of DMSO reduced the reaction time to half with a nominal increase in yield (entry 8, Table 1). Further, we were able to reduce the amount of DABCO to 2 equiv.

Using this procedure, we evaluated the substrate scope of this reaction (Table 2). The steric size and substitution pattern on

Table 2. Substrate Scope[a]

entry	product		time	% yield
1		**4a**	5 h	77
2		**4b**	5 h	73
3		**4c**	7 h	72
4		**4d**	8.5 h	71
5		**4e**	8 h	64[b]
6		**4f**	7.5 h	75[b]
7		**4g**	6 h	52
8		**4h**	4.5 h	70[c]
9		**4i**	6 h	34[b]

[a]All yields are average of two runs. Conditions: **3a–i** (1.0 equiv), **1** (3.0 equiv), DABCO (2.0 equiv), 60 °C. [b]3.5 equiv of **1** was used. [c]Reaction was run at 45 °C with 3.5 equiv of **1**.

the aryl ring had minimal impact on the yields (Table 2, **4a**, **4b**, **4c**, **4d**). To understand whether a nucleophilic aromatic system will result in acylation of the aromatic ring, we chose substrates with a dimethoxy aryl group and a thiophene-yl group. The corresponding products **4e** and **4f** were obtained in 64% and 75% yield, respectively. We were unable to detect any acylation of the aromatic ring. When an indole derivative was used as a substrate, the indole nitrogen had to be protected. In the

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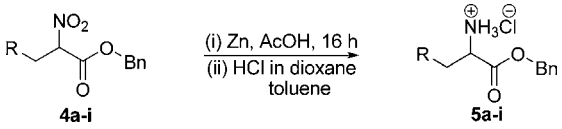
absence of a protecting group, the indole nitrogen reacts with the activated carbonate in a competing side reaction resulting in lower yields.[16] A pyridine ring was also tolerated, and the corresponding pyridyl nitro ester was synthesized in moderate yields. In this case, the reaction did not proceed in the absence of DABCO (see Supporting Information). Pyridylalanines have found extensive use in medicinal chemistry.[17] Homophenylalanine is an amino acid residue found in the inhibitor of angiotensin converting enzyme.[18] The corresponding α-nitro ester was synthesized using this method, albeit in low yields (**4i**, Table 2). All of the α-nitro esters were readily reduced to the corresponding α-amino esters in good yields using zinc and acetic acid (Table 3).[13a] To test the scalability of the α-nitro ester formation, we decided to synthesize **4a** on a 1 g scale. With practicality in mind, we avoided column purification of benzyl phenyl carbonate required for this reaction. Instead, we purified it by distillation. This material contained approximately 9% by mass of dibenzyl carbonate as an impurity. We used this carbonate in our large-scale reaction and obtained **4a** in ∼85% yield and ∼93% purity after a simple workup. Further purification of the product by chromatography resulted in isolation of ∼1.2 g (73%) of the product (Scheme 3).

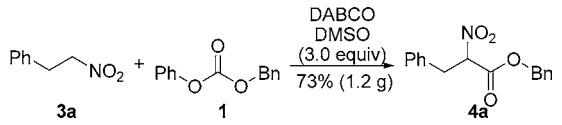
Table 3. Reduction of α-Nitro Esters to α-Amino Esters[a]



entry	substrate	product	% yield
1	**4a**	**5a**	88
2	**4b**	**5b**	84
3	**4c**	**5c**	85
4	**4d**	**5d**	84
5	**4e**	**5e**	82
6	**4f**	**5f**	85
7	**4g**[b]	**5g**	88
8	**4h**	**5h**	77
9	**4i**	**5i**	83

[a]Conditions: (i) Zn dust (6.0 equiv), AcOH; (ii) 4 M HCl in dioxane (1.6 equiv), toluene. [b]4.8 equiv of HCl was used; isolated as the dihydrochloride salt.

Scheme 3. Gram-Scale Synthesis of α-Nitro Ester



The reactivity pattern of nitronate anion in this reaction is different from what has been reported previously.[14] Nitronate anions are ambident nucleophiles that can react through either the carbon atom or the oxygen atom. In the case of alkyl halides, the dominant pathway is reaction through the oxygen atom with the exception of 4-nitrobenzyl chloride.[19,20] Reactivity through carbon has been accomplished under radical conditions.[21] In the case of aldehydes and imines, the nitronate anion reacts through the carbon atom.[22] The apparent dichotomy in reactivity has been explained using the hard and soft acids and bases (HSAB) concept. In this explanation, the softer carbon center of the nitronate anion is expected to react with softer π-electrophiles. The reported reactivity of nitronate anions with carbonates and similar electrophiles is contrary to what is expected based on the HSAB concept.[14] In these reactions, the harder oxygen atom of the nitronate anion reacts with the soft π-electrophile leading to the formation of a nitronocarbonate that undergoes an elimination to yield nitrile oxides. In contrast to the reported reactions of nitronate anions with carbonates, we observe formation of α-nitro esters. Mayr and co-workers have shown that the reactivity of nitronate anions with various electrophiles can be explained on the basis of the reversibility of attack through the oxygen atom.[23] Based on this, we believe that in our reaction the attack through oxygen atom is kinetically favored and reversible. The reversibility is engendered by the presence of DABCO, which converts the kinetically favored nitrono carbonate back to an activated carbonate and a nitronate anion. Teramura and co-workers have shown that nitroalkanes react with ethyl chloroformate in the presence of triethylamine, a non-nucleophilic base, to give nitrile oxides.[14b] This proceeds through the formation of a nitronocarbonate. In our case, we use a nucleophilic base that can potentially regenerate the nitronate anion from the nitronocarbonate. To further understand the irreversible nature of the α-nitro ester formation we performed an ^{1}H NMR study. This indicated that DABCO deprotonates the product nitro ester (see Supporting Information). This potentially makes the ester carbonyl inert to DABCO attack, therefore making this reaction irreversible.

In conclusion, we have developed a safe and scalable alternative to the Strecker reaction. We have utilized an easy-to-handle carbonate as a carboxyl equivalent. A reaction was performed on a gram scale without the need for extensive purification of the carbonate. The product α-nitro esters have been reduced readily to the corresponding α-amino esters. Using this procedure, β-aryl-α-amino esters can be accessed readily under mild conditions. This is in contrast to the procedures that utilize dianions of nitroalkane. The formation of α-nitro esters is mechanistically intriguing, as previous reports indicate that similar reactions give rise to nitrile oxides. Further research in our laboratory will focus on delineating the mechanism of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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