Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 5298

Received 22nd April 2021,
Accepted 26th May 2021

DOI: 10.1039/d1ob00786f

rsc.li/obc

Acetyl nitrate mediated conversion of methyl ketones to diverse carboxylic acid derivatives†

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The development of a novel acetyl nitrate mediated oxidative conversion of methyl ketones to carboxylic acid derivatives is described. By analogy to the haloform reaction and supported by experimental and computational investigation we propose a mechanism for this transformation.

Synthetic methodologies enabling the oxidative cleavage of carbon–carbon single bonds is an area of considerable recent interest.[1–7] The development of methodologies to achieve this transformation would be anticipated to be of significant utility by expanding substrate scope for oxidative C–C functionalization reactions in academic and industrial applications. Due to the high activation energy for this transformation and the ubiquitous nature of C–C bonds, strategies that achieve selective cleavages remain challenging. To overcome these challenges several methodologies have been developed including employing strained scaffolds,[8] chelation assisted reactions[3,4] and adjacent keto functionality.[5,6,9] Here we report a general strategy for the synthesis of carboxylic acid derivatives by oxidative cleavage of methyl ketones.

Aromatic carboxylic acid derivatives are prevalent structural motifs in drug molecules and materials. Synthetic access to these compounds is most commonly achieved by initial carboxylation of the corresponding arene, requiring strong oxidants (*e.g.* $KMnO_4$, chromium-based oxidants) and harsh reaction conditions.[10] Preparation of carboxylic acid derivatives requires a subsequent transformation of the carboxylic acid. Aromatic methyl ketones serve as an attractive alternative to aromatic carboxylic acids as they are readily available and can be efficiently prepared by acylation.[11,12] Conversion of this alternative substrate requires the oxidative cleavage of a C–C single bond. The most widely employed methodology to achieve this transformation, the well-known haloform reaction allows ready access to the corresponding carboxylic acids however does not allow for the direct assembly of other carboxylic acid derivatives.[10,13] Hence, a reaction enabling direct conversion of aromatic methyl ketones to a diverse array of carboxylic acid derivatives would be desirable.

Inspired by the reliability of the well-established haloform reaction[10,14] and based on early industrial studies on the reactivity of acetyl nitrate, we envisioned a process enabling the net oxidative C–C bond cleavage of aromatic methyl ketones.[15,16] Analogous to the haloform reaction this process was anticipated to proceed *via* a series of sequential α-nitration reactions and subsequent nucleophilic displacement of an activated di- or trinitromethane.[17–25] Contrasting the haloform reaction, in which the base (*e.g.* KOH) typically serves as nucleophile forming carboxylic acids we envisioned the ability to easily modulate the nature of the second nucleophile to allow direct access to a diverse array of carboxylic acid derivatives.

Acetyl nitrate, formed *in situ* by the reaction of nitric acid with acetic anhydride,[26] has been reported to mediate the acylation of acetoacetic esters in the presence of a protic or Lewis acid catalyst.[16] We initially evaluated the efficiency of α-nitration of 4-bromoacetophenone using *in situ* generated acetyl nitrate under acidic reaction conditions. Our initial screen evaluated the consumption of 4-bromoacetophenone and evaluated varying the stoichiometry of reagents and solvent (Table 1). We found that a minimum of 3.0 equiv. of acetyl nitrate was required to achieve <42% conversion of starting material (entries 1–4). The addition of a Lewis Acid additive (entry 5) provided minimal benefit however excess nitric acid (entries 6) provided a notable enhancement in the consumption of 4-bromoacetophenone to predominantly a single new chemical species by ^{1}H-NMR. We subsequently evaluated a series of potential solvents for the reaction (entries 6–10), of which acetonitrile (entry 9) provided the highest level of conversion in these evaluations.

Building on these observations we sought to isolate and fully characterize the species produced through the action of

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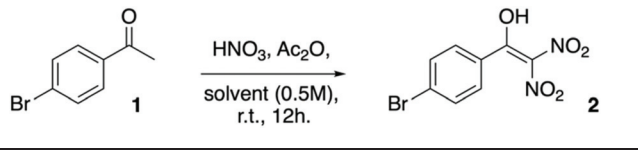
†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic analysis, computational details. See DOI: 10.1039/d1ob00786f

Table 1 Initial survey of the reaction of a methyl ketone with *in situ* generated acetyl nitrate[a]



Entry	HNO_3 (equiv.)	Ac_2O (equiv.)	Solvent (0.5 M)	% Conversion[b]
1	1	1	AcOH	2%
2	2	1	AcOH	15%
3	2	2	AcOH	15%
4	3	3	AcOH	42%
5[c]	3	3	AcOH	43%
6	6	3	AcOH	61%
7	6	3	THF	46%
8	6	3	DMSO	51%
9	6	3	MeCN	83%
10	6	3	DMF	0%

[a] Reactions were performed with **1** (1.0 equiv.), HNO_3, Ac_2O, additives in the indicated solvent (0.5 M). [b] All percent conversions were determined by monitoring the disappearance of the ^{1}H-NMR signal of 4-bromoacetophenone (δ 7.52, d). [c] With boron trifluoride diethyl etherate (0.1 equiv.).

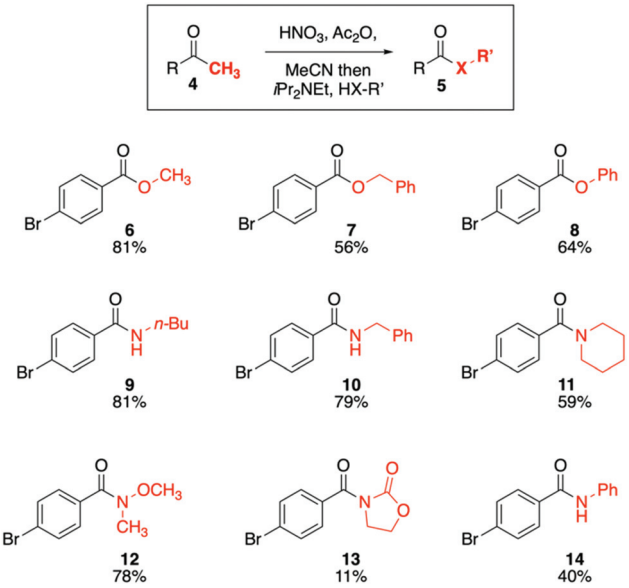


Fig. 1 One-pot acetyl nitrate-mediated conversion of methyl ketones to carboxylic acid derivatives. Examples varying the heteroatom nucleophile. Yield based on heteroatom nucleophile.

acetyl nitrate on 4-bromoacetophenone in the presence of excess HNO_3. In the reaction of 4-bromoacetophenone in MeCN with 6.0 equiv. HNO_3 and 3.0 equiv. Ac_2O, we were delighted to successfully isolate the product **2**, the enol tautomer of the desired dinitro methyl ketone.[27] While sufficient quantities of **2** could be purified by flash silica gel chromatography, this species proved to be reactive and readily converts to 4-bromobenzoic acid upon storage or exposure to water.

Having confirmed the production of a nitrated intermediate (*i.e.* **2**) through the action of acetyl nitrate on a methyl ketone, we sought to examine if this intermediate species could be trapped by the addition of a suitable nucleophile for the one pot conversion of a methyl ketone to carboxylic acid derivatives. Therefore, following reaction of the methyl ketone with HNO_3 and Ac_2O the reaction mixture was neutralized with i-Pr_2NEt and treated with an alcohol or amine nucleophile for the synthesis of esters and amides, respectively (Fig. 1). To our delight we found that oxygen-based nucleophiles effectively engaged the intermediate nitrated species in productive reaction. Beyond simply trapping the intermediate through the addition of water to provide a carboxylic acid, reactivity directly paralleling the haloform reaction, we found that aliphatic alcohols and phenol could be efficiently used directly providing esters **6–8**. Notably, these reactions proceed directly from the free alcohol, without the need for preformation of an alkoxide, demonstrating the electrophilicity of the dinitroketone intermediate. Additionally, we find that both primary and secondary aliphatic amines can be engaged in reaction to directly provide amides **9–11** in moderate to good yields. The Weinreb-Nahm amide[28,29] can be prepared in high yield providing an alternative strategy for the conversion of a methyl ketone into a differentially substituted ketone, complementing enolate alkylation.[30,31] Notably, even highly unreactive heteroatom nucleophiles including aniline and carbamates were competent in this process (**13** and **14**), however, with diminished yield.

With a range of heteroatom nucleophiles having been identified as competent in this transformation, we turned attention to evaluate some examples changing the structure of the methyl ketone (Fig. 2) . In addition to 4-bromo substituted

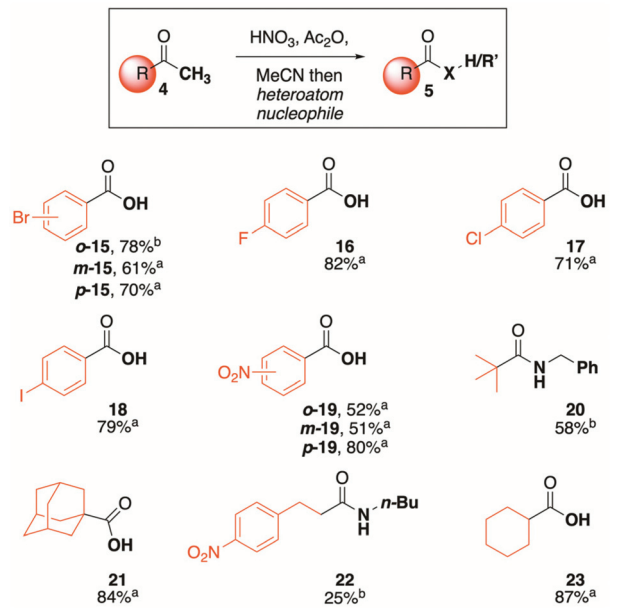


Fig. 2 One-pot acetyl nitrate-mediated conversion of methyl ketones to carboxylic acid derivatives. Examples varying the methyl ketone substrate. [a] Yield based on methyl ketone. [b] Yield based on heteroatom nucleophile.

aromatic methyl ketones other aromatic halogens are well tolerated (**15–18**). Further, the electron poor 2-nitro, 3-nitro and 4-nitro substituted methyl ketones engaged effectively in this reaction (**19**). Substrate scope for the methyl ketone was found to be limited for aromatic substrates in which ring nitration serves as a competing reaction process. For example; acetophenone, *para*-methoxy acetophenone and heterocyclic methyl ketones did not produce any desired product. Contrasting this limitation, aliphatic ketones were found to be capable of serving as substrates in this reaction with moderate to high efficiency. Alkyl ketones in which only one enol can form were converted into amides and carboxylic acids effectively (**20** and **21**). Alkyl ketones for which isomeric enols are possible proceeded with varying efficiency. In certain examples (*i.e.* **22**), providing only low yield of the desired product. However, in the case of cyclohexyl methyl ketone, this transformation proved reliable, providing **23** in high yield.

Having defined an acetyl-nitrate mediated process for the direct conversion of aromatic methyl ketones to a diverse array of carboxylic acid derivatives, we sought to further expand on the utility of this methodology in the synthesis of heterocycles from methyl ketones. We rationalized that the introduction of a bis-functionalized nucleophile may enable the one-pot oxidative conversion of methyl ketones to heterocycles and therefore evaluated the reaction with a di-amine and amino-alcohols (**24**, Fig. 3). Pleasantly, we found that this methodology proved useful in the synthesis of benzimidazole **26** and benzoxazoles **27–28** in moderate to excellent yields.

Based on our observations from the development of this reaction process and by analogy to the mechanism of the haloform reaction, we developed a proposed sequence of events for the current reaction (Fig. 4). Firstly, in reactions with *in situ* generated acetyl nitrate we observe the production of a dinitro enol, **34**. This intermediate, while sensitive to reaction with water and other heteroatom nucleophiles, is isolable, enabling characterization by ^{1}H-NMR and ^{13}C-NMR.[27] Therefore, we propose that keto to enol tautomerization of the starting material (**4**) precedes the reaction of enol **29** with *in situ* generated acetyl nitrate **30** to produce

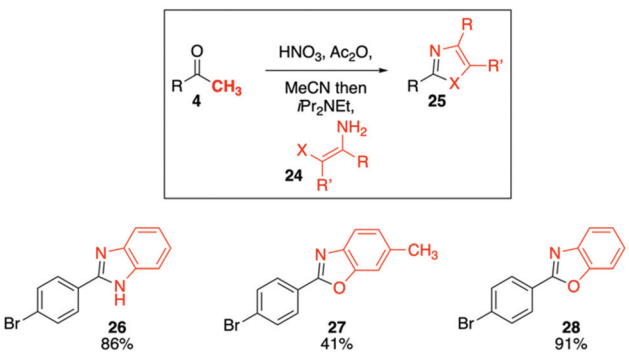


Fig. 3 One-pot conversion of an aromatic methyl ketone to heterocycles. Yield based on heteroatom nucleophile.

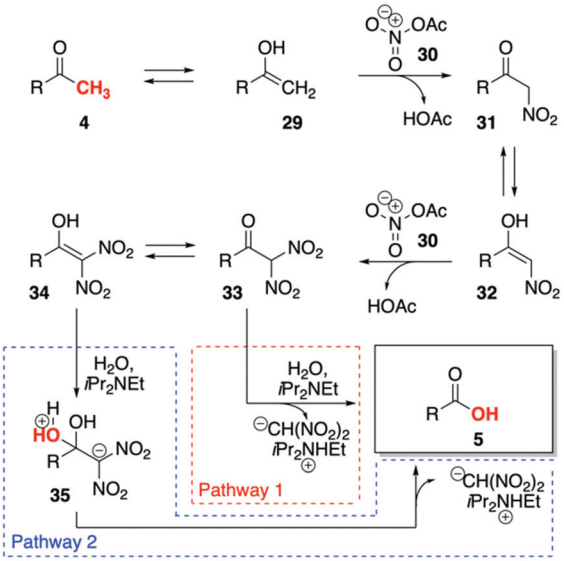


Fig. 4 Proposed mechanism for acetyl nitrate-mediated synthesis of carboxylic acid derivatives from methyl ketones.

mononitrated intermediate **31**.[32] The requirement for an additional acid additive is likely important in allowing for efficient enol formation for reaction with acetyl nitrate as the keto form of the starting material (**4**) will be favoured over the required enol form (**29**).[33] Subsequent enol formation from this mono-nitrated intermediate provides **32** which again reacts with acetyl nitrate to produce the penultimate dinitrated intermediate **33**. Our isolation and characterization of the enol tautomer of this ketone (**34**) and the absence of the keto tautomer of this species (**33**) by NMR analysis suggests that the enol tautomer of the dinitro ketone is thermodynamically favoured. We note that this contrasts the haloform reaction performed under acidic enol formation conditions in which each successive addition of halide further disfavours the formation of a nucleophilic enol. For this reason, the haloform reaction under acidic enol forming conditions is most widely employed for selective mono-halogenation of a ketone.[34] Contrasting the haloform, this reaction process may, in fact, favour additional nitration events and thereby enable haloform-like reactivity under acidic conditions where the traditional haloform reaction would not be successful.[14] We note that the dinitromethyl ketone **33**/**34** can undergo further nitration to produce a trinitromethyl ketone intermediate.[17] While we have not observed evidence to support the existence of this intermediate, we cannot fully exclude its formation. By contrast, we can isolate the dinitro intermediate **33**/**34** (*i.e.* **2**) and confirm that this intermediate proceeds to **6** upon exposure to water. Further, we have confirmed that dinitration is sufficient for carbon–carbon bond cleavage as propiophenone undergoes efficient oxidative C–C bond cleavage to produce the carboxylic acid (see ESI†).

Therefore, we hypothesize that the dinitro intermediate (**33**/**34**) may be operative in the addition of heteroatom nucleophiles, ultimately producing a diverse array of carboxylic acid

derivatives (**5**) with the expulsion of dinitromethane. This process could reasonably proceed from either/both of the tautomers, **33** and **34**.[15] To help distinguish between the two pathways (Fig. 4), we examined simplified versions of each pathway using acetophenone as our methyl ketone and hydroxide as the heteroatom nucleophile (Fig. 5). The modified **5**, **33**, **34**, and **35** ground states and were optimized using the wB97x-D DFT functional in the 6-31++G** basis set with solvent effects included using a PBF model for acetonitrile. The 2 transition states (**33-TS**, **34-TS**) were then obtained using the same functional, implicit solvent, and basis set. Considering the tautomers, we found that **33** is thermodynamically favoured over **34** by a free energy difference of 7.87 kcal mol^{-1}. This finding contrasts with the experimental result where only **34** tautomer was isolated.[35–38] To confirm this preference, we examined each tautomer with multiple functionals and a second basis set. Free energy differences and other electronic structure data for these calculations are available in the ESI.† We found that the preference for the **33** tautomer was robust over a variety of functionals and basis sets (see ESI†). Interestingly in one case, B3PW97-D3/6-31++G**, a much smaller free energy difference of 0.43 kcal mol^{-1} still in favour of **33** was observed. It may also be the case that the exclusive observation of the enol tautomer (*i.e.* **34**) is a result of substituent effects on relative enol/keto stability or solvent effects.[35–38] To investigate this, we also examined the free energy difference for **33**/**34** in an implicit chloroform solvent and found a very similar free energy difference of 8.79 kcal mol^{-1} in favour of the keto form (**33**). This result along with previous computational studies of keto/enol tautomers indict that implicit solvent DFT calculations alone are not enough to characterize the tautomer equilibrium.[36,37] We are currently seeking to better refine our understanding of the influence of stability differences between the enol and keto tautomers for both the haloform reaction as well as this transformation, including the possible impact of trace water complicating correlation of our experimental *vs.* computational studies and exploring the effect of including explicit solvent molecules.[37] We note that the energy difference between **33** and **34** is smaller than the transition state energy, accordingly both tautomers are predicted to be energetically accessible for this reaction.

Examining the first transition state for both pathways we find a free energy barrier of 18.1 kcal mol^{-1} from **34** to **35** and 30.4 kcal mol^{-1} for **33** to the products. The free energy barrier from **34** to **35**, mechanistically analogous to a Michael addition to an α,β-unsaturated nitroalkene, is 12.3 kcal mol^{-1} lower than the barrier for direct nucleophilic addition to the ketone **33**. This could suggest that the Michael addition pathway (pathway 2, Fig. 4) is overall favoured due to its lower free energy barrier for reaction, however, we were not successful in identifying a definitive transition state for **35-TS**. The scenario described here in which the dinitroenol **34** is rapidly equilibrating with ketone **33** however proceeds through a lower energy pathway to product would represent an example of Curtin-Hammett kinetics.[39] We note that while computationally we find the energy barrier lower for reaction from enol **34** the pathway from ketone **33** is viable based on the successful C–C bond cleavage in propiophenone which can not form the dinitroenol tautomer (see ESI†).

In summary, we have developed a new reaction that expands on the venerable haloform reaction. This reaction, mediated by acetyl nitrate, enables the one-pot conversion of methyl ketones into carboxylic acid derivatives and heterocycles. In this initial disclosure we have defined the scope and illuminated some mechanistic aspects of this new reaction process. Future studies will seek to address some of the limitations of the current reaction process, further expand the scope and applicability of this direct synthetic conversion of methyl ketones to a diverse array of carboxylic acid derivatives and continue to refine our understanding of the role of the relative stability of enol/keto tautomers in these processes.

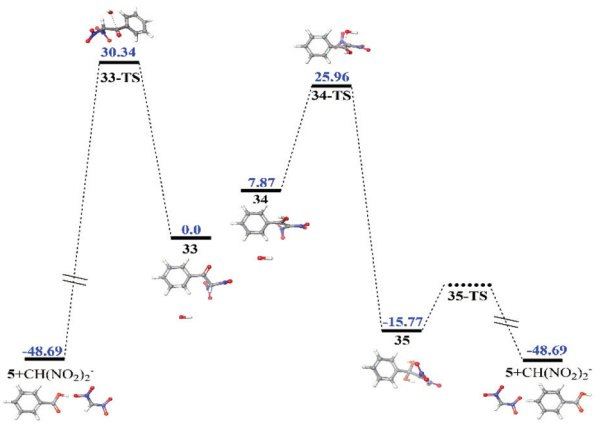


Fig. 5 Differences in total free energy between various states as compared to **33** + OH^-. Includes solvent and ZPE corrections. The product from both pathways is benzoic acid.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the New Jersey Health Foundation (PC104-77) and Rowan University for financial support.

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