Formyloxyacetoxyphenylmethane as an *N*-Formylating Reagent for Amines, Amino Acids and Peptides

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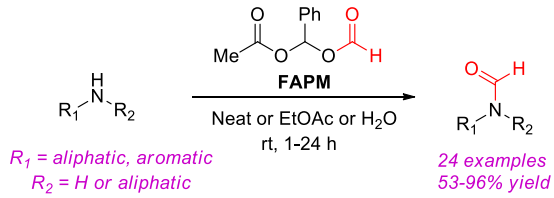


ABSTRACT: Formyloxyacetoxyphenylmethane is a stable, water-tolerant, *N*-formylating reagent for primary and secondary amines that can be used under solvent-free conditions at room temperature to prepare a range of *N*-formamides, *N*-formyl-anilines, *N*-formyl-α-amino-acids, *N*-formyl-peptides and an isocyanide.

N-Formylation reactions of primary and secondary amines are important transformations in organic chemistry, because they provide direct access to the highly versatile formamide group.[1] Highlighting their synthetic utility, *N*-formyl derivatives can be used as precursors for the synthesis of formamidines,[2] ureas,[3] carbamates,[3] aryl amides,[4] isocyanates,[5] nitriles[6] and isocyanides.[7] Consequently, they have often been used as intermediates for the synthesis of pharmaceuticals.[8] Alternatively, the *N*-formyl group may be used as a protecting group for peptide synthesis,[9] whilst many naturally occurring formamides exhibit important medicinal and biological activities.[10] The formamide moiety is also present in pharmaceuticals, including Leucovorin (chemotherapeutic),[11a] Formoterol (asthma)[11b] and Orlistat (anti-obesity).[11c]

Due to their importance, a number of *N*-formylating reagents for primary and secondary amines have been developed,[1] including the use of formic acid,[12a] formic acid in the presence of coupling reagents (e.g. DCC),[12b] acetic formic anhydride,[12c] formate esters,[12d] formamides,[12e] trialkylorthoformates,[12f] enol formates,[12g] ammonium formate,[12h] and *N*-formyl-benzotriazole.[12i] However, many of these reagents are only moderately reactive towards sterically hindered or electronically deactivated amines, often requiring elevated temperatures, extended reaction times or the use of excess reagent for their *N*-formylation reactions to proceed to completion.[1] A number of these formylating reagents are also susceptible to hydrolysis, whilst some reagents can decompose to liberate hazardous by-products (e.g. C≡O).[1] Given these limitations, a number of catalytic *N*-formylation protocols have also been developed that employ *N*-formyl donors in combination with acid catalysts, Lewis acids, organocatalysts, metal catalysts and biocatalysts.[13]

Given the limitations of using many *N*-formylating reagents under catalyst free conditions, we now report herein that formyloxyacetoxyphenylmethane (FAPM) **5** can be used as a bench-stable formylating reagent for primary/secondary amines under solvent-free conditions at room temperature. Importantly, the stability of FAPM **5** towards hydrolysis, enables it to be used as a catalyst free *N*-formylating reagent for α-amino acids and peptides in aqueous based solvent systems.

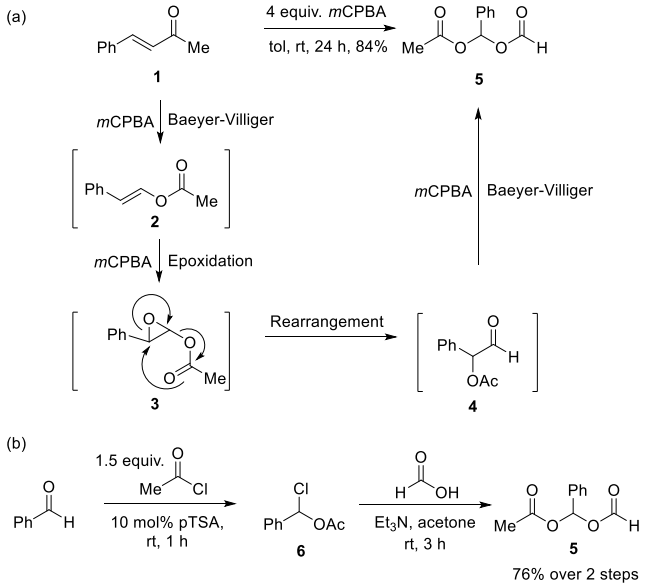
As part of investigations into the Baeyer-Villiger oxidation reactions of α,β-unsaturated ketones, we found that treatment of benzylidene acetone **1** with 4 equiv. of *meta*-chloroperoxybenzoic acid (*m*CPBA) in toluene for 24 h gave FAPM **5** in 84% isolated yield (Scheme 1a).[14] In this remarkable one-pot 4-step reaction, benzylidene acetone **1** first undergoes an *m*CPBA mediated Baeyer-Villiger reaction to afford enol acetate **2**, whose electron-rich alkene bond is then epoxidised by a second equivalent of *m*CPBA to afford epoxy-acetate **3**. This unstable epoxy-acetate **3** then undergoes intramolecular rearrangement to afford aldehyde **4**, which then undergoes a further *m*CPBA mediated Baeyer-Villiger reaction to afford FAPM **5**. The formation of intermediates **2** and **4** in this oxidation reaction were confirmed by ^{1}H NMR spectroscopic analysis of a series of control reactions that were carried out using fewer equivalents of *m*CPBA over shorter periods of time (see SI for details).[15]

A second route to FAPM **5** was also developed using a variant of a protocol previously developed by Raphaeli and coworkers for the synthesis of non-symmetric acyloxyalkyl esters.[16] This involved treatment of benzaldehyde with 1.5 equiv. of acetyl chloride in the presence of a catalytic amount of *para*-toluene sulfonic acid to afford α-chlorobenzyl acetate **6**,[17] that was subsequently reacted with formic acid andEt_3N in acetone to afford FAPM **5** in 76% yield (Scheme 1b).[18]

FAPM **5** proved to be a bench-stable liquid that could be stored at room temperature under nitrogen for up to 6 months without decomposition. We reasoned that FAPM **5** might act as a selective *N*-formyl donor for amines, which was confirmed by reacting 1.5 equiv. of FAPM **5** with 1 equiv. of benzylamine **7a** in THF at rt for 4.5 h to give *N*-formyl-benzylamine **8a** and imine **9**in 90% and 10% conversion respectively (Table 1, entry 1). Importantly, ^{1}H NMR spectroscopic analysis revealed no evidence of any *N*-acetyl-benzylamide having been formed *via* competing *N*-acyl transfer from FAPM **5**. Mechanistically, we propose that

benzylamine **10a** attacks the reactive formyl group of FAPM to irreversibly afford formamide **8a**,

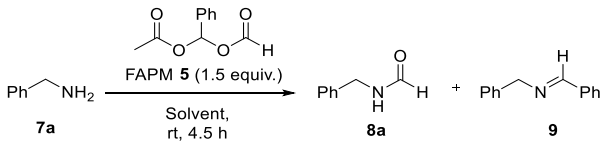
Scheme 1. Syntheses of formyloxyacetoxyphenylmethane**5** via: (a*) m*CPBA mediated oxidation reaction of benzylidene acetone **1**. (b) Nucleophilic attack of formic acid on α-chlorobenzyl acetate **6**.



with benzaldehyde and acetic acid being generated as by-products. Unwanted formation of imine **9** then occurs through acid catalyzed reaction of benzylamine **7a** with the benzaldehyde by-product. A solvent screen was carried out with the aim of identifying conditions that would suppress formation of imine **9.** Use of ethanol and 1,4-dioxane (Table 1, entries 2-3) also afforded significant amounts of the unwanted imine **9** by-product (8-12%). Carrying out the *N*-formylation reaction in MeCN (Table 1, entry 4) gave reduced amounts of imine (4%), whilst CH_2Cl_2, toluene and EtOAc (Table 1, entries 5-7) gave excellent conversion to *N*-formyl-benzylamine **8a** with only trace amounts of imine **9** (≤2%) being formed. Since imine formation is potentially reversible, a series of *N*-formylation reactions were carried out in mixed aqueous solvents, in the hope that the presence of bulk water would perturb the reaction equilibrium away from imine formation. Gratifyingly, use of 1:1 mixtures of THF : H_2O, MeCN : H_2O and 1,4-dioxane : H_2O (Table 1, entries 8-10) gave good conversions to *N*-formyl-benzylamine **8a**, with ≤1% of imine **9** being formed in each case. The tolerance of FAPM **5** towards hydrolysis in aqueous systems was confirmed by carrying out an *N*-formylation reaction in water,[19] with 1.5 equiv. of FAPM **5** resulting in complete conversion of benzylamine to *N*-formyl-benzylamine **8a** (Table 1, entry 11). Finally, FAPM **5** could also be used under solvent free conditions (Table 1, entry 12), resulting in clean *N*-formylation of benzylamine, with only 2% of imine **9** being produced.[20]

^{1}H NMR spectroscopic analysis of the *N*-formylation reaction of benzylamine in d_8-toluene revealed that complete consumption of benzylamine **7a** occurred after 1 h. Analysis after 15 min revealed the presence of a 87 : 13 mixture of formamide **8a** : imine **9**, which subsequently equilibrated to a 99 : 1 mixture of formamide **8a** : imine **9** after 1 hr. With this information in hand, we employed 1.5 equiv. of FAPM to *N*-formylate a range of sixteen primary and secondary amines **7a-** to afford a series *N*-formamides **8a-p** in 5396% yield after chromatographic purification (Scheme 2). Most of these *N*-formylation reactions were carried out under solvent-free conditions by dissolving the amine in neat FAPM and stirring at rt, followed by purification by silica chromatography. In those cases where the parent amine was insoluble in FAPM **5**, then EtOAc was employed as a cosolvent to afford a homogeneous reaction mixture. *N*-Formylation reactions of primary aliphatic amines proved particularly facile; typically affording their corresponding formamides **8a-e** in good to excellent yields (81-95%). Pleasingly, amines containing acid sensitive functionalities, such as furan and dimethyl acetal were well tolerated, affording formamides **8b** and

Table 1. Solvent screen to optimize the *N*-formylation reaction of benzylamine with FAPM **5**



Entry	Solvent	Formamide **8a**	Imine **9**
1	THF	90	10
2	EtOH	88	12
3	Dioxane	92	8
4	MeCN	96	4
5	CH_2Cl_2	100	-
6	Toluene	100	-
7	EtOAc	98	2
8	THF : H_2O (1 : 1)	99	1
9	MeCN : H_2O (1 : 1)	100	-
10	Dioxane : H_2O (1 : 1)	99	1
11	H_2O	100	-
12	Neat	98	2

Product ratios determined from integrals of diagnostic resonances for **8a** and **9** in ^{1}H NMR spectra of crude reaction products.

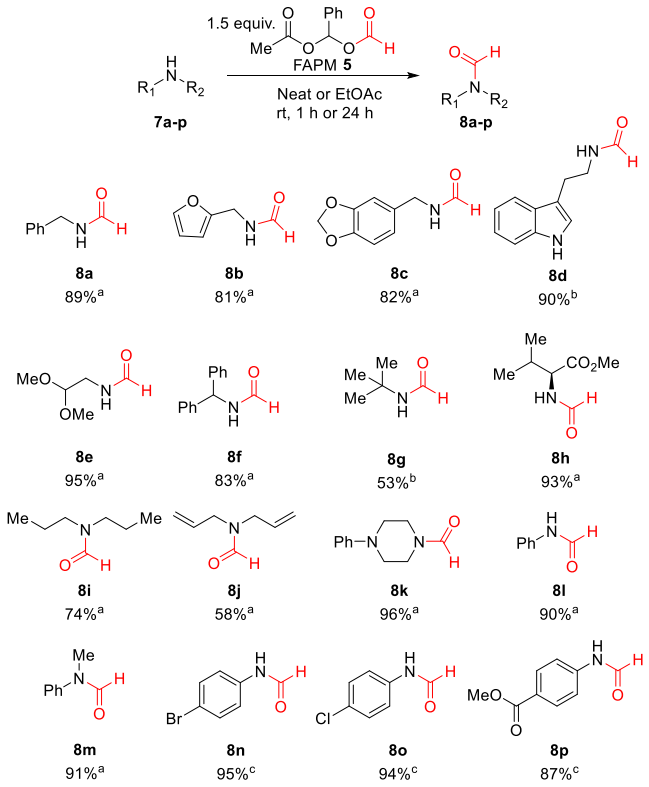
8e in 95% and 85% yields respectively. FAPM **5** reacted exclusively with the primary amine functionality of tryptamine to afford formamide **8d** in 90% yield. Whilst the formamide **8f** of sterically congested benzhydrylamine was formed in good 83% yield, formylation of *tert*-butylamine gave *N*-formamide **8g** in only 53% isolated yield, arising from losses during reaction work-up due to its volatility. (*S*)-Valine methyl ester afforded *N*-formamide **8h** in an excellent 93% yield, with no evidence of any racemization having occurred. Acyclic and cyclic secondary amines were also formylated using FAPM **5**, with moderate to excellent 58-96% yields of *N*-formamides **8i-k** being isolated. Pleasingly, electron-deficient aniline and its secondary *N*-methyl derivative gave their corresponding formamides **8l-m** in excellent 90% and 91% yields respectively. However, formylation of anilines containing deactivating halogen or ester groups required extended reaction times of 24 h for their corresponding *N*-formamides **8o-p** to be formed in 87-95 % yields respectively.

Alternative work-up procedures were then developed to allow for these *N*-formylation reactions to be carried out on-scale, without the need for chromatographic purification. When the desired formamide product was crystalline, or a high boiling oil, then the acetic acid and benzaldehyde by-products could be removed by fractional distillation *in vacuo*. For more volatile formamides, purification could be achieved by first extracting the crude reaction product with $NaHCO_{3(aq)}$ to remove acetic acid, followed by extraction with $NaHSO_{3(aq)}$ to remove benzaldehyde. This affords a crude product containing the formamide that is then purified by recrystallisation or fractional distillation as required (See SI for details).

Although several reagents have been developed for the *N*-formylation of amino ester derivatives,[21] extension of these

methods to unprotected α-amino acids has not been widely reported. This is due to the instability of many formylating reagents towards hydrolysis in aqueous media and the insolubility of α-amino acids in non-aqueous solvents. Currently, *N*-formyl-α-amino acids are most commonly prepared via treatment of the parent α-amino acids with a large excess of Ac_2O and formic acid (*via* formation of formyl acetate *in situ*), which often requires forcing conditions and/or extended reaction times.[22] *N*-formylation of α-amino acids using formic acid in water has been reported, however this protocol requires Oxyma as a stoichiometric coupling reagent.[22] Given the observed stability of FAPM in aqueous solvents, a range of six L-amino acids**10a-f** were treated with 1.5 equiv. of FAPM in water containing 5 equiv. of $NaHCO_3$ as a base, which resulted in 80-85% conversion to their corresponding formamides **11a-f** after 16 h. However, we subsequently found that modifying these formylation reactions, by incorporating addition of a second portion of FAPM **5** (1.5 equiv.) after 8 h, resulted in complete consumption of each α-amino acid, giving *N*-formyl-amino acids **11a-f** in good to excellent 71-89% isolated yields, with no racemization having occurred (Scheme 3).

Scheme 2: FAPM **5** as an *N*-formylating reagent for the synthesis of *N*-formamides **8a-p**

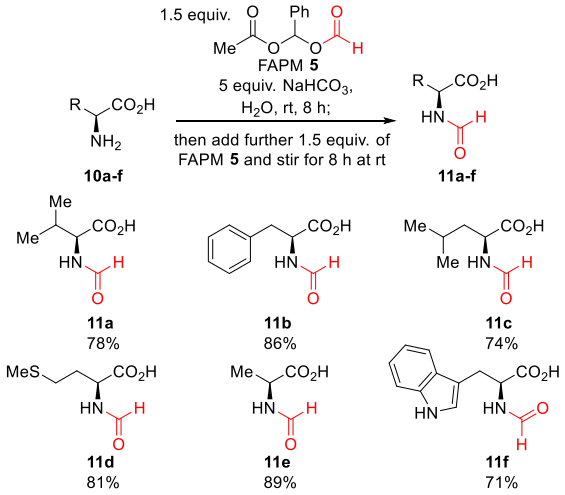


(a) Reaction conditions: 2 mmol of amine, 1.5 equiv. FAPM **5**, 1 h, rt. (b) Reaction conditions: 2 mmol of amine, 1.5 equiv. FAPM **5**, EtOAc, 1 h, rt. (c) Reaction conditions: 2 mmol of amine, 1.5 equiv. FAPM **5**, EtOAc, rt, 24 h.

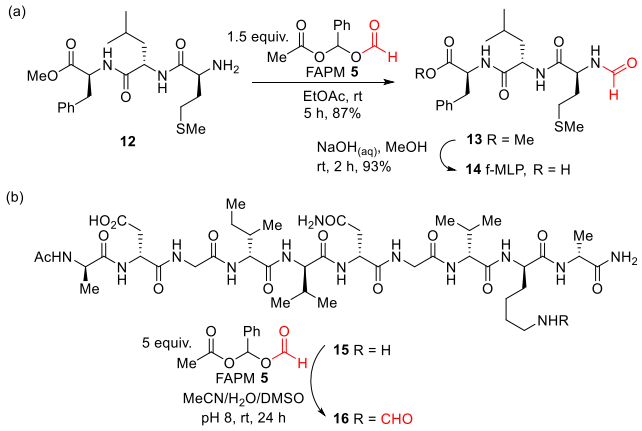
N-Formylmethionine-leucyl-phenylalanine (f-MLP) **14** is a chemotactic *N*-formyl-tripeptide that is a potent chemoattractant for leukocytes and a macrophage activator that is involved in triggering the innate immune response towards bacterial pathogens,[24] that was chosen as a suitable target to test the utility of FAPM for the *N*-formylation of peptidic substrates. The parent tripeptide ester **12** was treated with 1.5 equiv. of FAPM in EtOAc for 5 h to afford formamide **13** in 87% yield, which was then hydrolysed using NaOH/MeOH to afford f-MLP **14** in 93% yield (Scheme 4a). Similarly, a decapeptide with the sequence Ac-ADGIVNGVKA-NH_2 **15** containing *N*-acetamide and *C*-primary amide termini, was reacted with 5 equiv. of FAPM in a mixture of MeCN/H_2O (pH 8.0) containing a few drops of DMSO. This resulted in *N*-formylation of the free ω-amino group of its lysine residue affording *N*-formyl-decapeptide **16**, as confirmed from HRMS analysis (Scheme 4b).

Formamides are often employed for the synthesis of isocyanides,[7] and so we investigated whether FAPM **5** could be used to develop a stepwise 'one-pot' protocol to directly convert an amine into its corresponding isocyanide. 4-Bromoaniline **7n** and FAPM **5** (1.5 equiv.) were stirred in CH_2Cl_2 at rt for 24 h to afford its corresponding formamide **8n** *in situ* (confirmed by ^{1}H NMR spectroscopic analysis). Sequential dropwise addition of diisopropylamine (4 equiv.) and $POCl_3$ (1.2 equiv.) to this solution of formamide **8n** in CH_2Cl_2 at 0 °C, followed by stirring at 0 °C for 2 h and rt for 4 h, gave 1-bromo-4-isocyanobenzene **17**in 74% yield over two steps (Scheme 5).

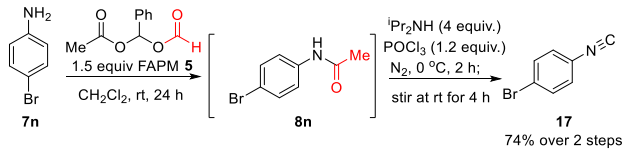
Scheme 3: FAPM **5** as an *N*-formylating reagent for the synthesis of *N*-formyl-α-amino acids **11a-f**.



Scheme 4. FAPM **5** for the synthesis of: (a) *N*-formylmethionyl-leucyl-phenylalanine (f-MLP) **14**; (b) *N*-formyl-decapeptide **16**



Scheme 5 FAPM **5** for the one-pot synthesis of isocyanide **17**



In conclusion, two practical syntheses of formyloxyacetoxyphenylmethane **5** have been developed and its use as a water toler-

ant *N*-formylating reagent for primary and secondary amines under solvent-free conditions demonstrated. Its potential as a reagent for the synthesis of *N*-formyl-α-amino acids and *N*-formyl-peptides in aqueous systems has been established and it has also been used as an *N*-formylating reagent in a one pot protocol to convert an aniline into its corresponding isocyanide.

ASSOCIATED CONTENT

Complete experimental procedure and relevant spectra (^{13}C and ^{1}H NMR spectra) for all compounds. 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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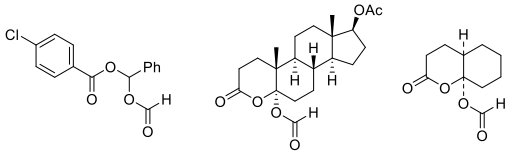

2.8 eq peracid, 16h, 20% **18** | 4 eq peracid, 84 h, 6% **19** | 3 eq peracid, 72 h, 66% **20**

15. A similar mechanistic rationale was proposed to explain formation of mixed acylals **19** and **20**; See refs 14b-c for details.
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