Organic LETTERS

Letter

pubs.acs.org/OrgLett

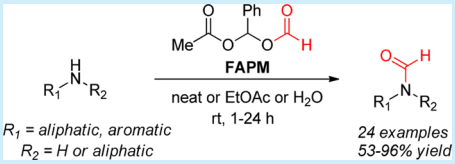
Formyloxyacetoxyphenylmethane as an *N*-Formylating Reagent for Amines, Amino Acids, and Peptides

Robert S. L. Chapman,[‡] Ruth Lawrence,[‡] Jonathan M. J. Williams, and Steven D. Bull*

Department of Chemistry, University of Bath, Bath BA2 7AY, U.K.

Supporting Information

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*-formylanilines, *N*-formyl-α-amino acids, *N*-formylpeptides, and an isocyanide.



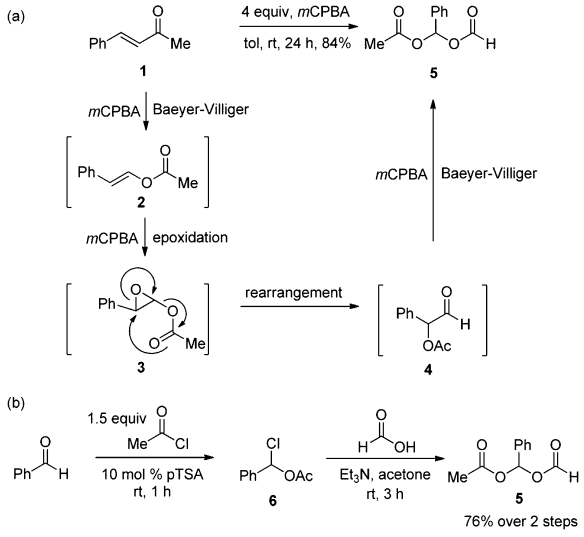
N-Formylation reactions of primary and secondary amines are important transformations in organic chemistry because they provide direct access to the highly versatile formamide group.[1] Highlighting their synthetic utility, *N*-formyl derivatives can be used as precursors for the synthesis of formamidines,[2] 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] while 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 (antiobesity).[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] *N*-formyl-saccharin,[12e] trialkyl orthoformates,[12f] enol formates,[12g] ammonium formate,[12h] and *N*-formylbenzotriazole.[12i] However, many of these reagents are only moderately reactive toward 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, while some reagents can decompose to liberate hazardous byproducts (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 Brønsted 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**) toward 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 our investigations into the Baeyer–Villiger oxidation reactions of α,β-unsaturated ketones, we found that treatment of benzylidene acetone **1** with 4 equiv of *m*-chloroperoxybenzoic acid (*m*-CPBA) in toluene for 24 h gave FAPM (**5**) in 84% isolated yield (Scheme 1a).[14] In this remarkable one-pot, four-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 epoxidized 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

Scheme 1. Syntheses of Formyloxyacetoxyphenylmethane 5 via (a) *m*-CPBA-Mediated Oxidation Reaction of Benzylidene Acetone 1 and (b) Nucleophilic Attack of Formic Acid on α-Chlorobenzyl Acetate 6



Received: August 1, 2017

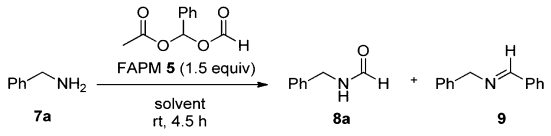
DOI: 10.1021/acs.orglett.7b02382
Org. Lett. XXXX, XXX, XXX–XXX

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 the Supporting Information (SI) for details).[15]

A second route to FAPM (**5**) was also developed using a variant of a protocol previously developed by Rephaeli and co-workers for the synthesis of nonsymmetric acyloxyalkyl esters.[16] This involved treatment of benzaldehyde with 1.5 equiv of acetyl chloride in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford *α*-chlorobenzyl acetate **6**[17] that was subsequently reacted with formic acid and Et_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*-formylbenzylamine **8a** and imine **9** in 90% and 10% conversion, respectively (Table 1, entry 1).

Table 1. Solvent Screen To Optimize the *N*-Formylation Reaction of Benzylamine with FAPM 5[a]



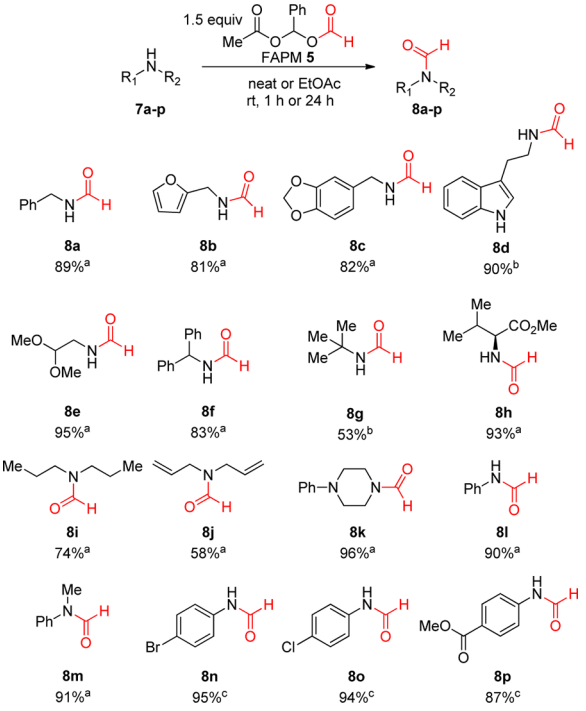
entry	solvent	formamide **8a**	imine **9**
1	THF	90	10
2	EtOH	88	12
3	dioxane	92	8
4	MeCN	96	4
5	CH_2Cl_2	100	
6	toluene	100	
7	EtOAc	98	2
8	THF/H_2O (1:1)	99	1
9	$MeCN/H_2O$ (1:1)	100	
10	$dioxane/H_2O$ (1:1)	99	1
11	H_2O	100	
12	neat	98	2

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

Importantly, ^{1}H NMR spectroscopic analysis revealed no evidence of any *N*-acetylbenzylamide 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**, with benzaldehyde and acetic acid being generated as byproducts. Unwanted formation of imine **9** then occurs through acid-catalyzed reaction of benzylamine **7a** with the benzaldehyde byproduct (see the SI for reaction mechanism). 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 and 3) also afforded significant amounts of the unwanted imine **9** byproduct (8–12%). Carrying out the *N*-formylation reaction in MeCN (Table 1, entry 4) gave reduced amounts of imine (4%), while CH_2Cl_2, toluene, and EtOAc (Table 1, entries 5–7) gave excellent conversion to *N*-formylbenzylamine **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 $1,4\text{-dioxane}/H_2O$ (Table 1, entries 8–10) gave good conversions to *N*-formylbenzylamine **8a**, with ≤1% of imine **9** being formed in each case. The tolerance of FAPM (**5**) toward 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*-formylbenzylamine **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 h. With this information in hand, we employed 1.5 equiv of FAPM to *N*-formylate a range of 16 primary and secondary amines **7a–p** to afford a series *N*-formamides **8a–p** in 53–96% yield after chromatographic purification (Scheme 2). Most of these *N*-formylation reactions

Scheme 2. FAPM 5 as an *N*-Formylating Reagent for the Synthesis of *N*-Formamides 8a–p[a]



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

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**), 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

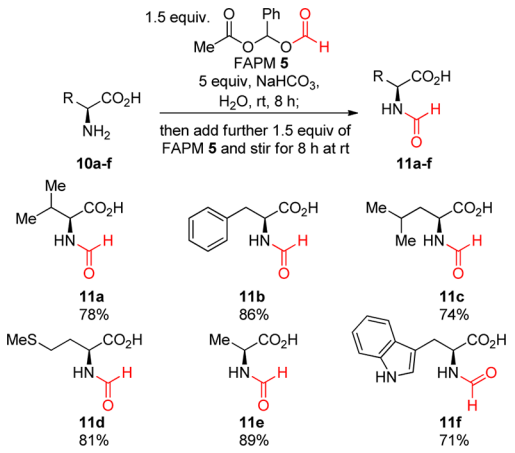
DOI: 10.1021/acs.orglett.7b02382
Org. Lett. XXXX, XXX, XXX–XXX

to excellent yields (81−95%). Pleasingly, amines containing acid-sensitive functionalities, such as furan and dimethyl acetal, were well tolerated, affording formamides **8b** and **8e** in 81% and 95% yields, respectively. FAPM (**5**) reacted exclusively with the primary amine functionality of tryptamine to afford formamide **8d** in 90% yield. While 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 workup 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 workup procedures were then developed to allow these *N*-formylation reactions to be carried out on scale, without the need for chromatographic purification (see the SI for details).

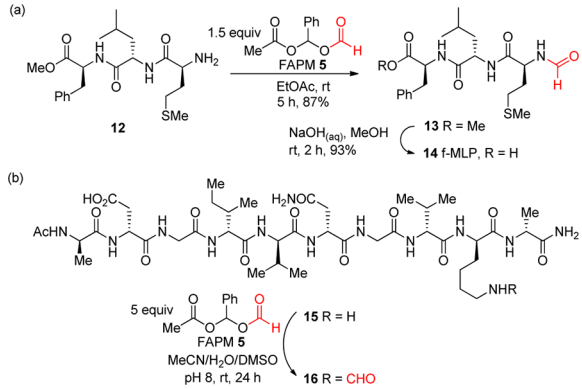
Although several reagents have been developed for the *N*-formylation of amino ester derivatives,[21] extension of these methods to unprotected α-amino acids has not been widely reported. This is due to the instability of many formylating reagents toward hydrolysis in aqueous media and the insolubility of α-amino acids in nonaqueous 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.[23] 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*-formylamino acids **11a−f** in good to excellent 71−89% isolated yields, with no racemization having occurred (Scheme 3).

N-Formylmethioninelecucylphenylalanine (f-MLP, **14**) is a chemotactic *N*-formyltripeptide that is a potent chemoattractant for leukocytes and a macrophage activator that is involved in triggering the innate immune response toward bacterial pathogens.[24] Consequently, it 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 hydrolyzed 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*-formyldecapeptide **16**, as confirmed from HRMS analysis (Scheme 4b).

Scheme 3. FAPM 5 as an *N*-Formylating Reagent for the Synthesis of *N*-Formyl-α-amino Acids 11a−f

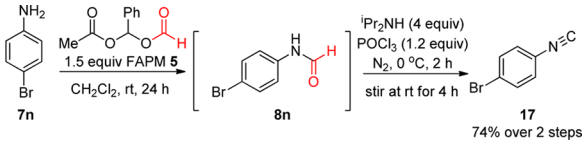


Scheme 4. FAPM 5 for the Synthesis of (a) *N*-Formylmethionylleucylphenylalanine (f-MLP) 14 and (b) *N*-Formyldecapeptide 16



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 ^1H 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 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-tolerant *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*-formylpeptides in aqueous systems has been established, and it

DOI: 10.1021/acs.orglett.7b02382
Org. Lett. XXXX, XXX, XXX−XXX

has also been used as an *N*-formylating reagent in a one-pot protocol to convert an aniline into its corresponding isocyanide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02382.

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: s.d.bull@bath.ac.uk.

ORCID

Steven D. Bull: 0000-0001-8244-5123

Author Contributions

‡R.S.L.C. and R.L. contributed equally.

Notes

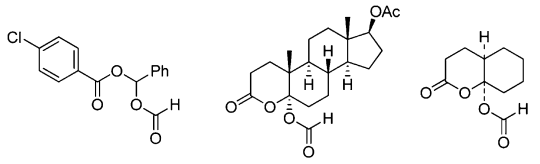
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Bath, EPSRC, and the Centre for Doctoral Training in Sustainable Chemical Technologies (EP/L016354/1) for funding. We thank Dr. Jody Mason (Department of Biology, University of Bath) for donating a sample of decapeptide **15** that was prepared using conventional solid-phase peptide synthesis.

■ REFERENCES

(1) Gerack, C. J.; McElwee-White, L. *Molecules* **2014**, *19*, 7689−7713.
(2) Han, Y.; Cai, L. S. *Tetrahedron Lett.* **1997**, *38*, 5423−5426.
(3) Faraj, M. K. Synthesis of isocyanate precursors from primary formamides. U.S. Patent 5,686,645, 1997.
(4) Jo, Y.; Ju, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2009**, *74*, 6358−6361.
(5) Fu, P. P.; Boyer, J. H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2246−2250.
(6) Arlt, D.; Klein, G. Preparation of nitriles from formamides. U.S Patent 4419297, 1983.
(7) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, *1985*, 400−402.
(8) Jackson, A.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1319.
(9) Yamashiro, D.; Li, C. H. *J. Org. Chem.* **1973**, *38*, 2594−2597.
(10) Wright, A. D.; Lang-Unnasch, N. *J. Nat. Prod.* **2009**, *72*, 492−495.
(11) (a) Machover, D. *Cancer* **1997**, *80*, 1179−1187. (b) Hett, R.; Fang, Q. K.; Gao, Y.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **1998**, *2*, 96−99. (c) Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, *8*, 4497−4500.
(12) (a) Jung, S. H.; Ahn, J. H.; Park, S. K.; Choi, J. K. *Bull. Korean Chem. Soc.* **2002**, *23*, 149−150. (b) Tornesello, A. L.; Sanseverino, M.; Buonaguro, F. M. *Molecules* **2016**, *21*, 736−742. (c) Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081−1118. (d) Christensen, S. B.; Hansen, A. M.; Franzyk, H. *J. Pept. Sci.* **2017**, *23*, 410−415. (e) Cochet, T.; Bellosta, V.; Greiner, A.; Roche, D.; Cossy, J. *Synlett* **2011**, *2011*, 1920−1922. (f) Kaboudin, B.; Khodamorady, M. *Synlett* **2010**, *2010*, 2905−2907. (g) Neveux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197−1199. (h) Reddy, P. G.; Kumar, G. D. K.; Baskaran, S. *Tetrahedron Lett.* **2000**, *41*, 9149−9151. (i) Katritzky, A. R.; Chang, H. X.; Yang, B. Z. *Synthesis* **1995**, *1995*, 503−505.
(13) (a) Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* **2010**, *51*, 2319−2322. (b) Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 3202−3205. (c) Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2010**, *51*, 4186−4188. (d) Habibi, D.; Nasrollahzadeh, M.; Sahebekhtiari, H. *J. Mol. Catal. A: Chem.* **2013**, *378*, 148−155. (e) Kim, J. G.; Jang, D. O. *Synlett* **2010**, *2010*, 2093−2096. (f) Deutsch, J.; Eckelt, R.; Kockritz, A.; Martin, A. *Tetrahedron* **2009**, *65*, 10365−10369. (g) Sonawane, R. B.; Rasal, N. K.; Jagtap, S. V. *Org. Lett.* **2017**, *19*, 2078−2081. (h) Patre, R. E.; Mal, S.; Nilkanth, P. R.; Ghorai, S. K.; Deshpande, S. H.; El Qacemi, M.; Smejkal, T.; Pal, S.; Manjunath, B. N. *Chem. Commun.* **2017**, *53*, 2382−2385. (i) Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652−6654. (j) Allen, C. L.; Atkinson, B. N.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1383−1386. (k) Ma'mani, L.; Sheykhan, M.; Heydari, A.; Faraji, M.; Yamini, Y. *Appl. Catal., A* **2010**, *377*, 64−69.
(14) For previous reports where peracid-mediated Baeyer−Villiger reactions of α,β-unsaturated ketones gave mixtures of products containing formyl acylals **18**−**20**, see the following. (a) Formyl acylal **18**: Baures, P. W.; Eggleston, D. S.; Flisak, J. R.; Gombatz, K.; Lantos, I.; Mendelson, W.; Remich, J. J. *Tetrahedron Lett.* **1990**, *31*, 6501−6504. (b) Formyl acylal **19**: Gorodetsky, M.; Danieli, N.; Mazur, Y. *J. Org. Chem.* **1967**, *32*, 760−764. (c) Formyl acylal **20**: DeBoer, A.; Ellwanger, R. E. *J. Org. Chem.* **1974**, *39*, 77−83.



(15) A similar mechanistic rationale was proposed to explain formation of mixed acylals **19** and **20**; see ref 14b,c for details.
(16) Nudelman, A.; Levovich, I.; Cutts, S. M.; Phillips, D. R.; Rephaeli, A. *J. Med. Chem.* **2005**, *48*, 1042−1054.
(17) Su, W. K.; Can, J. *J. Chem. Res.* **2005**, *2005*, 88−90.
(18) Formyl acylals have been prepared previously in moderate 44−57% yields via reaction of aldehydes with an acid anhydride and formic acid in the presence of phosphorus pentoxide; see: Scheeren, J. W.; Tax, W. J. M.; Schijf, R. *Synthesis* **1973**, *1973*, 151−153.
(19) For other *N*-formylation reactions in water, see: (a) Habibi, D.; Sahebekhtiari, H.; Nasrollahzadeh, M.; Taghipour, A. *Lett. Org. Chem.* **2013**, *10*, 209−212. (b) See Ref 12f.
(20) For other noncatalyzed solvent-free *N*-formylation reactions, see: (a) Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* **2010**, *51*, 2896−2899. (b) Habibi, D.; Nasrollahzadeh, M. *C. R. Chim.* **2013**, *16*, 1008−1016. (c) Dhake, K. P.; Tambade, P. J.; Singhal, R. S.; Bhanage, B. M. *Green Chem. Lett. Rev.* **2011**, *4*, 151−157. (d) Lebleu, T.; Kotsuki, H.; Maddaluno, J.; Legros, J. *Tetrahedron Lett.* **2014**, *55*, 362−364. (e) Batuta, S.; Begum, N. A. *Synth. Commun.* **2017**, *47*, 137−147.
(21) (a) Nishikawa, Y.; Nakamura, H.; Ukai, N.; Adachi, W.; Hara, O. *Tetrahedron Lett.* **2017**, *58*, 860−863. (b) El Dine, T. M.; Evans, D.; Rouden, J.; Blanchet, J. *Chem. - Eur. J.* **2016**, *22*, 5894−5898. (c) Hill, D. R.; Hsiao, C. N.; Kurukulasuriya, R.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 111−113. (d) Suchy, M.; Elmehriki, A. A. H.; Hudson, R. H. E. *Org. Lett.* **2011**, *13*, 3952−3955. (e) Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H. J. *Synthesis* **1996**, *1996*, 37−38. (f) Kim, J.-G.; Jang, D. O. *Synlett* **2010**, *2010*, 1231−1234. (g) Chancellor, T.; Morton, C. *Synthesis* **1994**, *1994*, 1023−1025.
(22) (a) Fayol, A.; Housseman, C.; Sun, X. W.; Janvier, P.; Bienaymé, H.; Zhu, J. P. *Synthesis* **2005**, *2005*, 161−165. (b) Yang, P.-Y.; Liu, K.; Ngai, M.-H.; Lear, M. J.; Wenk, M. R.; Yao, S. Q. *J. Am. Chem. Soc.* **2010**, *132*, 656−666. (c) Soriano-Maldonado, P.; Rodriguez-Alonso, M. J.; Hernandez-Cervantes, C.; Rodriguez-Garcia, I.; Clemente-Jimenez, J. M.; Rodriguez-Vico, F.; Martinez-Rodriguez, S.; Las Heras-Vazquez, F. J. *Process Biochem.* **2014**, *49*, 1281−1287.
(23) Aleiwi, B. A.; Mitachi, K.; Kurosu, M. *Tetrahedron Lett.* **2013**, *54*, 2077−2081.
(24) Yang, K. H.; Fang, H.; Ye, J. S.; Gong, J. Z.; Wang, J. T.; Xu, W. F. *Pharmazie* **2008**, *63*, 779−783.

DOI: 10.1021/acs.orglett.7b02382
Org. Lett. XXXX, XXX, XXX−XXX