Metal-Free Oxyacetoxylation of Arylynamines and Ynamides to Construct α-Acetoxyl Amides

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Abstract: Ynamides/arylynamines are challenging substrates for oxyacetoxylation, especially due to various reactive sites of *N*-heteroaryl ring. Herein we report a metal-free $PhI(OAc)_2$-mediated oxyacetoxylation of arylynamines / ynamides to provide α-acetoxyl amides in good to excellent yields. The transformation completes in a short time to afford solely the product without functionalising *N*-heteroaryl moiety, in a highly regio- and chemo-selective manner through β-iodo keteneiminium intermediate.

Introduction

α-Acetoxyl amide motifs widely exist in many natural products,[1] *e.g.*, compound **1** from *Strychnos Henningsii*[1a] and canthinone alkaloid **2** as PTP1B inhibitor (Figure 1).[1b] They serve as versatile intermediates in organic synthesis and widespread synthetic applications in the total synthesis of natural products, *e.g.*, *(-)-Isatisine A*.[2] They can be converted to α-hydroxy amides, which can be found in the structure of many relevant pharmacological compounds, *e.g.*, *Actinophyllic acid* and *Strychnocarpine*.[3] Various methods for synthesizing α-acetoxyl amides including Baeyer−Villiger epoxidation−ring-opening−intramolecular acyl transfer cascade,[4a,4b] multicomponent Passerini reactions,[4c-d] acylation of amine using 2-alkoxy acetic acid have been developed.[4e] Despite these advances, developing efficient methods for construction of α-acetoxyl amides is still in need.

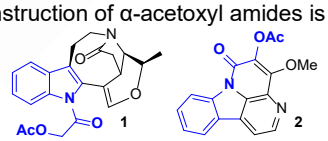


Figure 1. Natural products containing α-acetoxyl amides.

$PhI(OAc)_2$-mediated[5] oxyacetoxylation of standard terminal alkynes,[6] assisted by acetic acid,[6a] neighbouring group,[6b and 6c] or metal catalysts has recently emerged as an alternative methodology towards α-acyloxyketone synthesis;[6d-i] However, there are few reports on reaction of ynamides with $PhI(OAc)_2$ apart from Baell's report on iodoacyloxylation of ynamides to provide iodoenolamides.[7] Ynamides and ynamines would be expected to benefit from oxyacetoxylation by $PhI(OAc)_2$ to deliver α-acetoxyl amides, but they are more challenging substrates from a reactivity standpoint: ynamines and ynamides are moisture-sensitive and prone to hydration;[4a] secondly, they play the role of both the electrophilic and nucleophilic partner, can produce various complex upon Lewis acid catalysis, including dimerised adduct α-alkynyl enamide, trimerised adduct as well as polymer.[8a-c] In addition, subjecting ynamides to indole **3** can generate α-indolyl enamides **5**, arising from nucleophilic addition to *in situ* generated keteneiminium intermediates

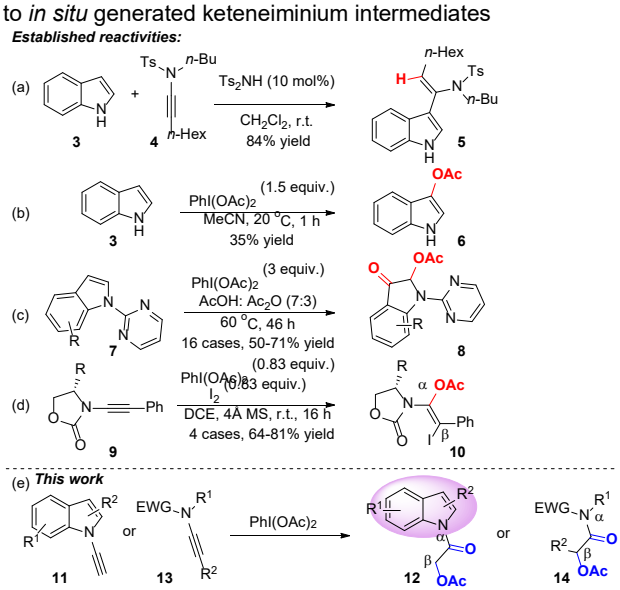


Figure 2. Established reactivities and the concept of this work.

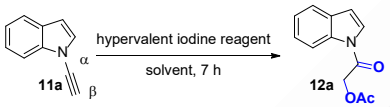
(Figure 2(a));[8d] Furthermore, controling chemoselectivity of acetoxylation on arylynamines can be difficult as the double bond on indole ring can also be functionalised by $PhI(OAc)_2$ (Figure 2(b) and (c)).[8e-g]

As part of a program[9] aimed at the development of new applications of ynamides and arylynamines in organic synthesis, we became interested in oxyacetoxylation of ynamides and arylynamines for the following reasons. First, while acetoxylation occurs at α position to the nitrogen atom in Baell's work (Figure 2 (d)),[7] inverse regioselectivities have been observed in the addition of acetoxyl group to ynamides / arylynamines, *i.e.*, at β-position of the triple bond (Figure 2(e)). Second, acetoxylation occurs chemoselectively at the triple bond while keeping the *N*-heteroaryl ring intact. Herein we report a highly regio- and chemoselective metal-free oxyacetoxylation of aryl ynamines and ynamides.

Results and Discussion

We started with oxy-sulfonyloxylation of terminal indolyl ynamine **11a** with less electrophilic diphenyliodonium triflate to avoid side-reactions (Table 1). CuI-bipy and CuCl-bipy were employed as catalyst[6f and 6h] to facilitate the reaction at room temperature; However, no desired oxysulfonyloxylative product was observed, either the ynamine decomposed, or an ynaminyl triflate was formed (Table 1, entries 1 and 2), probably arising from nucleophilic acetylenic displacement through generating ynaminyl (phenyl)iodonium salt.[10] Catalyst-free condition offered no benefit, no reaction occurred at room temperature (entry 3), and acetylindole was formed at an elevated temperature (entry 4), presumably coming from hydration of ynamine by small amount of HOTf generated from diphenyliodonium triflate.[11] Changing the counterion did not promote the reaction either (entries 5 and 6). The reaction proceeded slowly at room temperature to deliver desired oxyacetoxylative product **12a** in low yield 16% (entry 7) with most of the starting material left, accompanied by a series of byproducts: indole, hydrative product acetylindole, indolyl ynaminyl acetate and a complex mixture of inseparable side-products. Pleasingly, elevating temperature led to an improvement in oxyacetoxylation yield (66%) with reduced amount of byproducts (entries 8 to 11). As shown in entry 22, the yield dropped when using water as mixed solvent. Therefore, we speculated that moisture in organic solvents hydrolyses hypervalent iodine partially.[12] Followingly this, the equivalent of $PhI(OAc)_2$ was increased to 2 equivalents to compensate for the hydration. The conversion was indeed improved, and the yield was enhanced slightly (entry 10, compared to entries 13 and 14). Upon solvent screening, including non-hydroxy-containing and hydroxy-containing solvents (entries 16 to 23), we noticed that the reaction is compatible with various solvents, and the use of polar solvents improved the solubility of hypervalent iodonium salt, lea-

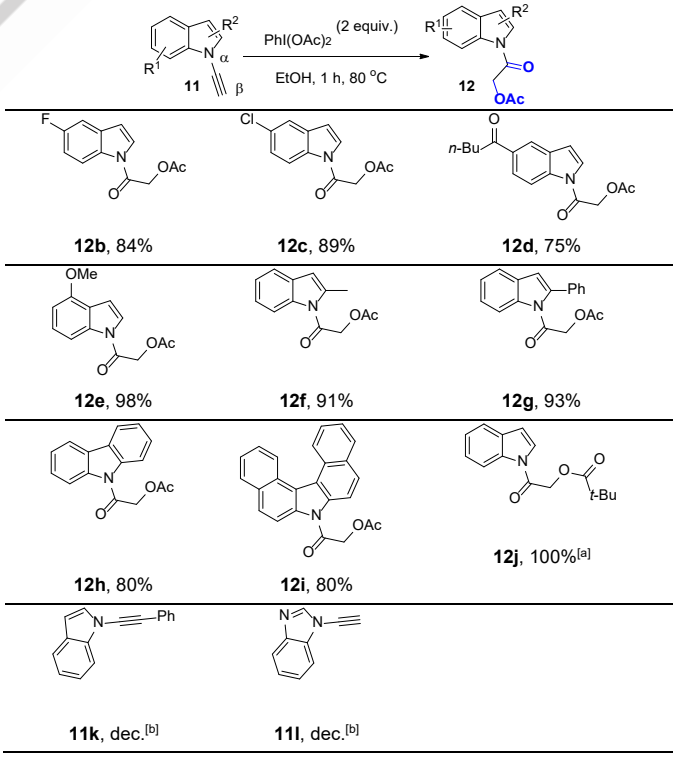
Table 1. Optimisation of conditions.[a]



entry	HVI (equiv.)	T (°C)	solvent	yield (%)[b]
1[c]	Ph_2IOTf (1)	r.t.	1,4-dioxane	dec.[d]
2[e]	Ph_2IOTf (1)	r.t.	1,4-dioxane	—[f]
3	Ph_2IOTf (1)	r.t.	1,4-dioxane	N.R.[g]
4	Ph_2IOTf (1)	80	1,4-dioxane	—[h]
5	Ph_2ICl (1)	80	1,4-dioxane	N.R.[g]
6	Ph_2IOAc (1)	80	1,4-dioxane	N.R.[g]
7[i]	$PhI(OAc)_2$ (2)	r.t.	1,4-dioxane	16
8[i]	$PhI(OAc)_2$ (2)	40	1,4-dioxane	38
9[j]	$PhI(OAc)_2$ (2)	60	1,4-dioxane	54
10	$PhI(OAc)_2$ (2)	80	1,4-dioxane	66
11	$PhI(OAc)_2$ (2)	100	1,4-dioxane	41
12	$PhI(OAc)_2$ (0.5)	80	1,4-dioxane	30
13	$PhI(OAc)_2$ (1)	80	1,4-dioxane	51
14	$PhI(OAc)_2$ (1.5)	80	1,4-dioxane	56
15	$PhI(OAc)_2$ (2.5)	80	1,4-dioxane	61
16	$PhI(OAc)_2$ (3)	80	1,4-dioxane	57
17[k]	$PhI(OAc)_2$ (2)	80	toluene	42
18	$PhI(OAc)_2$ (2)	80	THF	59
19	$PhI(OAc)_2$ (2)	80	MeCN	49
20[l]	$PhI(OAc)_2$ (2)	80	DCE	62
21[m]	$PhI(OAc)_2$ (2)	80	EtOH	94
22[m]	$PhI(OAc)_2$ (2)	80	EtOH/H_2O (1:1)	66
23[m]	$PhI(OAc)_2$ (2)	80	*i*-PrOH	92

[a] **11a** (0.2 mmol) in solvent (2 mL) for 7 h unless otherwise stated. [b] isolated yield. [c] CuI-bipy (10 mol%, 1:1). [d] dec. = decomposition. [e] CuCl-bipy (10 mol%, 1:1). [f] indolyl ynaminyl triflate was formed. [g] no reaction. [h] 1-acetylindole was formed; [i] reaction stirred for 24 hours. [j] reaction stirred for 15 h. [k] reaction stirred for 36 hours. [l] reaction stirred for 2 hours. [m] reaction stirred for 1 hour.

Scheme 1. Substrate exploration with respect to arylynamines.



[a] $PhI(OCOt\text{-}Bu)_2$ was used instead of $PhI(OAc)_2$. [b] Decomposition.

ding to full conversion of ynamine and shortened reaction time (1 h in entries 21 and 23 compared to 36 h in toluene entry 17).

With the optimised conditions in hand, the scope of the reaction was explored with respect to arylynamine (Scheme 1). For indole-derived ynamines, both electron-withdrawing and electron-donating groups (**12b-e**) as well as substituents on pyrrole ring (**12f-g**) were tolerated. The reaction provided products with acetoxylation exclusively at the β-position of the triple bond, leaving the indole ring intact. Apart from **11d** that afforded a small amount of substituted indole, all the other substrates in Scheme 1 gave solely the expected product in good to excellent yields, with electron-donating group (EDG)-substrates delivering products (**12e-g**) in higher yields than the electron-withdrawing group (EWG)-counterparts (**12b-d**). Carbazole- and dibenzocarbazole-substituted ynamines, with the electron pair of the nitrogen atom delocalised more widely over aromatic rings, still delivered high yields of products **12h** and **12i**. The addition of sterically hindered *di*-(pivaloyloxy)iodobenzene also worked well to provide quantative yield of oxyacyloxy product **12j**. By comparison, the use of an internal arylynamine (**11k**) and a less electron-rich ynamine, benzimidazole derivative (**11l**), failed to produce desired product, with ynamines decomposed. The configuration of oxyacetoxylative product was confirmed by single crystal X-ray diffraction of **12g** in Figure 3.[13]

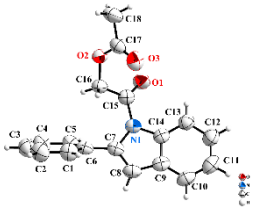
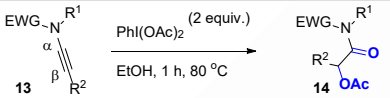
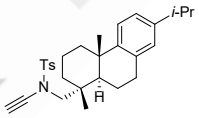


Figure 3. X-ray crystal structure of **12g** (CCDC 2165432) showing thermal ellipsoids at the 50% probability level.

Investigation of the scope with respect to the ynamide was also undertaken (Table 2). Benzyl ynamide displayed slightly different behaviours from those of arylynamine: apart from ynamide containing an electron-deficient fluorobenzyl group that formed α-acetoxyl amide in modest yield (**14f**, 54%), all benzyl ynamides, containing EDG (entries 1 to 5 and 8) and EWG groups (entries 7, 9 and 10), afforded products **14** in excellent yields. As noted, when ynamide was replaced by less electron-withdrawing esters (Ms, Boc) or by electron-donating alkyl substituted-ynamide (**13n**) to render the alkyne more nucleophilic, the reaction was less efficient: the use of Ms-derivant led to a moderate reduction in yield (entry 11, 69%), while **13n** and **13p** decomposed probably due to their over-reactivities. By contrast, when a less electron-donating, phenyl ynamide **13q** was employed, oxyacetoxylation did not occur, indicating the balance of electron-density of ynamide is crucial to impart the reaction. As such, the reaction was subjected to benzyl sulfonyl ynamide. We hypothesised that an alternative solution to suppress overreactivity of alkyl substituted-ynamides might be sterical shielding of the triple bond. Interestingly, when natural product dehydroabietylamine, featuring a neighbouring all-carbon quaternary centre, was introduced into the alkyl ynamide **13l**, the reaction proceeded extremely fast within 5 minutes to provide **14l** in high yield (84%) without side-products observed, which probably benefits from sterical influence by quaternary carbon on dehydroabietyl moiety. Noticeably, internal ynamide **13m**, ending with Me group, also delivered regioselective oxyacetoxylative product, albeit in moderate yield, while internal ynamide **13o**, ending with sterical rigid phenyl group, did not undergo the reaction.

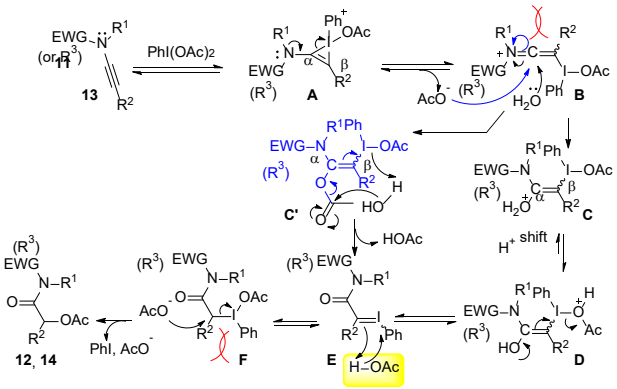
Table 2. Substrate exploration with respect to ynamides.



entry	starting material **13**			**14**	yield (%)
	R^1	EWG	R^2		
1	Bn	Ts	H	**14a**	96
2	*p*-$MeC_6H_4CH_2$	Ts	H	**14b**	98
3	*3,5*-$Me_2C_6H_3CH_2$	Ts	H	**14c**	99
4	*p*-$OMeC_6H_4CH_2$	Ts	H	**14d**	98
5	*p*-$PhC_6H_4CH_2$	Ts	H	**14e**	96
6	*p*-$FC_6H_4CH_2$	Ts	H	**14f**	54
7	*p*-$ClC_6H_4CH_2$	Ts	H	**14g**	85
8	Bn	Mbs[a]	H	**14h**	98
9	Bn	*p*-$ClC_6H_4SO_2$	H	**14i**	96
10	Bn	Ns	H	**14j**	98
11	Bn	Ms	H	**14k**	69
12[b]				**14l**	84
13	Bn	Ts	Me	**14m**	47
14	Cy	Ts	H	**14n**	dec.[c]
15	2-oxazolidinone		Ph	**14o**	N.R.[d]
16	Bn	Boc	H	**14p**	dec.[c]
17	Ph	Ts	H	**14q**	N.R.[d]

[a] Mbs = *p*-methoxybenzenesulfonyl. [b] Stirred for 5 minutes. [c] decomposition. [d] no reaction.

Conventional metal-free oxyacetoxylation pathway is initiated by alkynyliodonium salts through deprotonation of standard terminal alkynes, then followed by acetate addition to triple bond.[14] By contrast, the successful case of internal ynamide



Scheme 2. Proposed mechanism.

13m suggests it would be unlikely to proceed through formation of alkynyliodonium salts. In Scheme 2, $PhI(OAc)_2$ would instead preferentially coordinate with the triple bond chemoselectively

rather than the double bond delocalised in *N*-heteroaryl ring, owing to alkyne's electron-rich property imparted by adjacent electron-donating nitrogen atom. π-Acid activation of the ynamine / ynamide by $PhI(OAc)_2$ forms a highly electrophilic cyclopropenyl iodonium complex **A**,[7,15] which is followed by fragmentation on **A** to afford β-iodo keteneiminium intermediate **B** as a single regioisomer, due to the intrinsic polarisation of the ynamide. Owing to its high electrophilicity, this is followed by nucleophilic addition of trace amount of water from solvent or acetate to produce α-oxonium, β-iodo enamide/enamine **C** or α-acetoxyl, β-iodo enamide/enamine **C'**. The intramolecular proton transfer and consecutive elimination of acetic acid delivers iodonium ylide **E**, which alternatively could be provided by hydrolysis of ester from **C'**. Acidolysis of **E** yields alkyliodonium salt **F**. Substitution of the iodonium moiety by AcO^- finally gives α-acetoxyl amides. The introduction of amide group in the product has reduced the electron-density of *N*-heteroaryl ring, therefore presumably keeping *N*-aryl inactive on acetoxylation. As steric influence of R^2 (H, Me and Ph) magnifies, steric clash caused by R_2 and R_1 in **int-B** reinforces, as does that in **int-F**, accouting for the dropped reactivity of internal ynamine **11k**, ynamides **13m** and **13o**.

The success of oxyacetoxylation in non-hydroxy-containing solvents (entries 16 to 20 in Table 1) demonstrates that the oxygen source for oxyacetoxylation does not come from the hydroxy group of ethanol. Hence we employed extra dry acetonitrile to rule out ethanol, bearing hydroxy group, and moisture from solvent, as the possible oxygen sources. We conducted $H_2{}^{18}O$ isotopic-labeling experiment in order to track the source of oxygen for forming the product (Figure 4). Interestingly, both the ^{16}O- and ^{18}O-labeled oxyacetoxylative products were detected, along with indole and a complex mixture of inseparable side-products.[16] This shows that both $PhI(OAc)_2$ and $H_2{}^{18}O$ can be oxygen source, which further reveals that moisture from organic solvents could attack β-iodo keteneiminium intermediate **B** in Scheme 2. Meanwhile, a small amount of $^{18}O_2$-labeled product was observed, which might arise from nucleophilic substitution to ^{18}O-labeled **int-F** by $MeCO^{18}O^-$, released from hydrolysis of acyl enamidyl ester **C'**.

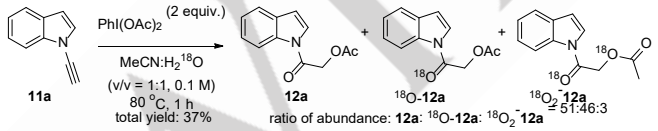


Figure 4. Experiment for mechanistic study.

The oxyacetoxylation has been scaled up to test reproducibility of the reaction (Figure 5). Product **12j** was obtained in satisfying yield by recrystallisation without chromatography. This approach provides a facile method to access α-acyloxy amides by a simple operation and shows potential industrial application.

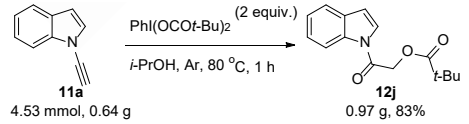


Figure 5. scale-up synthesis.

Conclusion

In conclusion, we have developed a metal-free oxyacetoxylation of arylynamines and ynamides to afford α-acetoxyl amides in generally good yields. While the intrinsic polarisation of ynamine/ynamide is crucial to achieve heightened reactivity and regioselectivity as well as chemoselectivity, steric hindrance influences the reactivity of ynamine/ynamide to some extent. Future work will target developments of this methodology in natural product synthesis.

Experimental Section

Oxyacetoxylation of ynamides or ynamines were performed under nitrogen atmosphere. Commercially available reagents were used throughout without further purification other than those detailed below. Solvents are AR grade. THF and toluene were distilled over sodium benzophenone ketyl under nitrogen atmosphere, 1,4-dioxane, acetonitrile and 1,2-dichloroethane were distilled over calcium hydride. EtOH was distilled over magnesium sulfate. Extra dry acetonitrile was purchased from commercial company Energy Chemicals. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker Avance 400 operating at 400 MHz for ^1H NMR and ^{13}C NMR at 100 MHz, or using Bruker Advance 500 spectrometer at 500 MHz for ^1H NMR and ^{13}C NMR at 125 MHz, or using Bruker Advance 600 spectrometer at 600 MHz for ^1H NMR and ^{13}C NMR at 150 MHz. $CDCl_3$ was used as the solvent for samples. ^1H NMR chemical shifts are reported using residual proton on non-deuterated solvent ($CDCl_3$: 7.26 ppm), whereas ^{13}C NMR spectra are reported using the carbon signals of the deuterated solvent ($CDCl_3$: 77.16 ppm). Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate solution as appropriate. All chromatography was carried out using silica gel (300-400 mesh) obtained from Qingdao Puke company. The removal of solvent was performed on a rotary evaporator in vacuum. High resolution mass spectrometry was carried out on a new ultraflextreme equipped with TOF/TOF/Ultimate 3000 Nano HPLC. Crystal evaluation and data collection were performed at room temperature on a Bruker APEX2 CCD area detector diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å, sealed X-ray tube. Using Olex2,[17] the structure was solved with the ShelXS[18] structure solution program using charge flipping and refined with the ShelXL[19] refinement package using least-squares minimization. All nonhydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms on the structure were placed in idealised positions and refined using a riding model.

General procedure: To an oven dried 10 mL Schlenk tube was charged arylynamine or ynamide 0.2 mmol in ethanol (2 mL). $PhI(OAc)_2$ (2 equiv.) was added and the mixture was stirred at 80 °C for 1 hour. After concentration *in vacuo*, the mixture was purified by column chromatography (*n*-hexane/EA) to give the corresponding product.

Additional references cited within the supporting information.[17-29]

Acknowledgements

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Keywords: oxyacetoxylation • metal-free • regioselective • chemoselective • ynamines / ynamides

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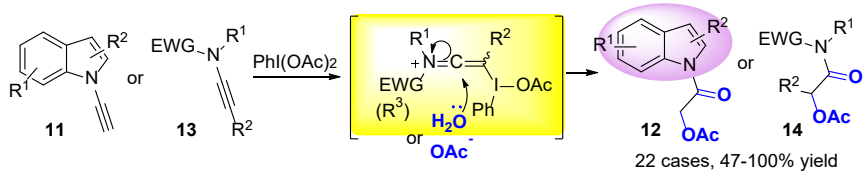

Herein we report a metal-free $PhI(OAc)_2$-mediated oxyacetoxylation of arylynamines and ynamides in good to excellent yields to provide α-acetoxyl amides in highly regio- and chemo-selective manner, leaving *N*-heteroaryl rings intact.