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Probing the reactivity of *o*-phthalaldehydic acid/ methyl ester: synthesis of *N*-isoindolinones and 3-arylaminophthalides[†]

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A new method for the synthesis of *N*-substituted isoindolinones and 3-arylaminophthalides was developed through aza-Wittig/ cyclisation. The reaction of *o*-phthalaldehydic acid methyl ester with benzylic, aromatic and aliphatic azides gave *N*-isoindolinones whereas reaction of *o*-phthalaldehydic acid with the aromatic azides gave 3-arylaminophthalides.

N-Substituted isoindolinone derivatives are heterocyclic compounds with a γ -lactam skeleton that have generated considerable interest due to their varied biological activities; anti-inflammatory,¹ antibacterial,² anxiolytic,³ inhibition of protein–protein interactions⁴ and HIV-reverse transcriptase inhibition.⁵ Furthermore, they are also known to exhibit fluorescent properties, which renders them useful as chemical probes.⁶

Synthetic approaches to isoindolinones include condensation reaction of amines with isobenzofuranone,⁷ o-phthalaldehyde,⁸ 2-bromomethylbenzoyl methylester,9 reduction of phthalimides,10 and lactamisation.¹¹ Metal-catalysed approaches include Pd-catalysed C-H activation of N-alkoxybenzamides,12 Pt-catalysed reductive coupling,13 Cu-catalysed multicomponent synthesis14 and o-lithiation/cyclisation.¹⁵ Other methods include N-capping of amines,16 electrophilic cyclisation,17 and radical cyclisation.18 We were interested in the substrates o-phthalaldehyde, o-phthalaldehydic acid, o-phthalaldehydic acid methylester derivatives as convenient starting points for a one-pot method. The condensation reaction of o-phthalaldehyde with amines resulted in N-isoindolinones,^{8a} whereas aza-Wittig reaction with azides gave both N-isoindolinones and their corresponding bis-products.¹⁹ The reaction of o-phthalaldehydic acid with aromatic amines may proceed *via* the semi-aminol to give 3-arylaminophthalides,²⁰ whereas under reductive C-N coupling conditions13 gave N-isoindolinones presumably via an intermediate amine. The reaction of immobilized o-phthalaldehydic acid ester with amines at higher temperatures gave 3-hydroxyisoindolinones via semi-aminol,

whereas at room temperature *N*-isoindolinones *via* imine were afforded.¹¹ Ghosh *et al.*,²¹ reported a mild method exploring reductive amination/cyclisation using *o*-phthalaldehydic acid methyl/thiomether ester derivatives and demonstrated that *o*-phthalaldehydic acid methyl ester derivative was less reactive. The subtle reactivity difference between the *o*-phthalaldehyde derivatives bearing aldehyde, acid, and methylester gives a different reaction pathway resulting in either *N*-isoindolinones or 3-substituted phthalides (Scheme 1).

During our recent investigations, we found that when a Wittig reaction of *o*-phthalaldehydic acid methylester **1** was carried out, it gave decomposed products, whereas *o*-phthalaldehydic acid **5** gave the corresponding olefins.²² In this paper, we investigate the aza-Wittig/cyclisation reaction of methylester **1** and *o*-phthalaldehydic acid **5** resulting in a novel synthesis of *N*-isoindolinones/3-substituted phthalides respectively (Scheme 1).

We first investigated the reactivity of *o*-phthalaldehydic acid methyl ester derivative **1**. Substrate **1** and benzyl azide **2a** were subjected to aza-Wittig/cyclisation reaction using triphenylphosphine in various solvents. The reaction time was optimised by performing the reactions at different time intervals for aza-Wittig reaction before the addition of reducing agent, NaBH₃CN for reductive cyclisation. These reactions revealed that solvent THF was optimal with a 6 h reaction time (Table 1).

Once the reaction conditions were optimised, we explored various benzylic, aromatic and aliphatic azides. These reactions revealed that: (i) benzylic azides **2a–d** and aliphatic azide **2e**



Scheme 1 Synthesis of N-isoindolinones and 3-arylaminophthalides.

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Table 1 Optimisation of aza-Wittig/cyclisation reaction



EDC = ethylene dichloride. ^{*a*} All the reactions were carried with **1** (0.2 mmol), azide **2a** (0.3 mmol) and PPh₃ (0.4 mmol) in solvent (5.0 mL) and stirred overnight after the addition of NaBH₃CN. ^{*b*} Reaction time before addition of NaBH₃CN. ^{*c*} Isolated yields.

gave the corresponding N-isoindolinones 4a-e exclusively, (ii) phenyl azide 2f, p-substituted aromatic azides 2g, i gave N-isoindolinones whereas 2h gave both isoindolinone 4h and the amine derivative 3h, (iii) *m*-substituted aromatic azides 2j-l resulted in the formation of N-isoindolinones 4j-l along with secondary amine derivatives 3j-l, probably due to electronic effects of azides or intermediate secondary amines formed during the reactions, (iv) o-substituted aromatic azides 2m, n and bulky aromatic azide 20 gave secondary amines 3m-o exclusively and the formation of corresponding isoindolinones 4m-o were not observed, this can be attributed to steric factors (Table 2). These electronic or steric effects were not observed in earlier reports where a condensation reaction of aromatic amines with o-phthalaldehyde was performed.^{8a} It was observed that amines 3h, 3j-l and 3o were unstable and converted to their corresponding isoindolinones on standing. To overcome the difficulty in purification due to contamination of triphenylphosphine oxide that was formed during the reactions, we explored the use of polymer-bound triphenylphosphine as an alternate strategy for the synthesis of isoindolinones.

We performed an aza-Wittig reaction of **1** with **2a** in THF using polymer-bound triphenylphosphine for 3 h followed by the addition of NaBH₃CN and optimised the reaction conditions. An analogous trend was observed for various azides when subjected to aza-Wittig reaction using polymer-bound triphenylphosphine (Table 3). Benzylic **2a**, **b**, aliphatic **2e** and *p*-substituted aromatic azide **2g** gave *N*-isoindolinones exclusively, whereas azide **2h** and *m*-substituted aromatic azides **2j**, **k** gave the corresponding secondary amines. Moreover, these reactions indicated that benzylic azides **2a**, **b**, and aliphatic azide **2e** required less time for cyclisation than aromatic azides **2g**, **h**, **j**, **k** (Table 3), which might be due to the higher reactivity of secondary amines formed during the reaction. The scope of the reaction was successfully demonstrated by exploring various substituted *o*-phthalaldehydic derivatives (Table 3, entries 8–10).

Our success in probing the reactivity of methyl ester **1** by aza-Wittig reaction prompted us to examine the reactivity of *o*-phthalaldehydic acid derivative **5**, which was in equilibrium with its corresponding lactol. Thus, subjecting acid **5** to aza-Wittig reaction with aromatic azides **2f**, **g**, **j**, and **2m** resulted in the isolation of 3-arylaminophthalides (Table 4, entries 3–6).

Table 2	Aza-Wittig/	cyclisation	reaction	with	various	azides ^a

OMe			OMe OMe O				
CO ₂ Me PPh ₃							
Ļ	1 CHO 2_{9-0}	NaBH ₃ CN	L i	R			
1 24-0			3a-0 4a-0				
			Product ra	v: 110 (o/)			
Entry	Azides	Time ^s (h)	3 (%)	4 (%)	Yield ^e (%)		
1		Me 12	3b (00)	4b (100)	72		
2	N ₃	12	3c (00)	4c (100)	55		
3		d 12	3d (00)	4d (100)	86		
4	N ₃ 2e CO ₂	₂ Et ¹²	3e (00)	4e (100)	69		
5	N ₃ -{>2	f 24	3f (00)	4f (100)	95		
6	$N_3 \rightarrow 0$	Me 48	3g (00)	4g (100)	94		
7	$N_3 \rightarrow C_{2h}$	PPh 48	3h (13)	4h (64)	77		
8	N ₃ -	F 48 2i 48	3i (00)	4i (100)	80		
9		2 j 48 le	3j (32)	4j (63)	95		
10		k 48	3k (23)	4k (69)	92		
11	N ₃	48	3l (32)	4l (57)	89		
12	N ₃ -21	n 48	3m (100)	4m (00)	75		
13	$N_3 \rightarrow 2$	n 48	3n (100)	4n (00)	55		
14	N ₃ -2	o 48	30 (100)	40 (00)	42		

^{*a*} All the reactions were stirred at RT for 6 h before the addition of NaBH₃CN. ^{*b*} Time required for reductive cyclisation. ^{*c*} Isolated yields.

Notably, similar reactions with benzylic azide **2a** and aliphatic azide **2e** have failed to give the corresponding 3-arylaminophthalides (Table 4, entries 1, 2); consistent with earlier experiments conducted with corresponding amines.²⁰ The structures of the 3-arylaminophthalides were confirmed by comparison of the spectral data with the authentic compounds prepared using a literature procedure.²⁰

Our findings indicate that isoindolinones prepared by aza-Wittig reaction using methyl ester 1 was *via* amine intermediate 'C' not the iminium ion 'D' (Scheme 2). The formation of 3-arylaminophthalides using *o*-phthalaldehydic acid 5 could

 Table 3
 Aza-Wittig reactions using polymer-bound triphenylphosphine^a



^{*a*} Conditions: **1** (0.1 mmol), azide **2a** (0.2 mmol) and polymer-bound PPh₃ (0.2 mmol) in THF (2.5 mL), RT, 3 h, then filter the resin, added NaBH₃CN (0.2 mmol). ^{*b*} Reaction time for cyclisation at reflux temperature. ^{*c*} Reaction time for cyclisation at RT. ^{*d*} Reaction performed in MeOH at reflux temperature. ^{*e*} Isolated yields.

Table 4 Aza-Wittig/cyclisation reaction using o-phthalaldehydic acid^a



 a Conditions: 5 (0.15 mmol), azide 2a (0.3 mmol) and polymer-bound PPh₃ (0.3 mmol), MeOH (5.0 mL), reflux, 5 h. b Reaction using PPh₃. c Isolated yields.



Scheme 2 Proposed mechanism for aza-Wittig/cyclisation reaction of *o*-phthalaldehydic acid/methyl ester derivatives.

be *via* intermediate 'E'. However, it can be argued that it could be formed *via* aromatic amines generated from the corresponding azides at higher temperatures in protic solvents such as MeOH.²³ To probe this issue, reaction of 5 with **2f** was conducted in the aprotic solvent, THF, which resulted in isolation of the corresponding 3-arylaminophthalide **6f**. This suggests the reaction proceeded *via* aza-Wittig adduct (Scheme 2).

In summary, a new entry into the synthesis of *N*-substituted isoindolinones and 3-arylaminophthalides was developed through aza-Wittig/cyclisation reaction. The reaction of *o*-phthalaldehydic acid methyl ester with azides gave novel *N*-isoindolinones and the electronic and steric effects were investigated. Reaction of *o*-phthalaldehydic acid with aromatic azides gave novel 3-arylaminophthalides, whereas reaction with benzylic and aliphatic azides failed.

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