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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.

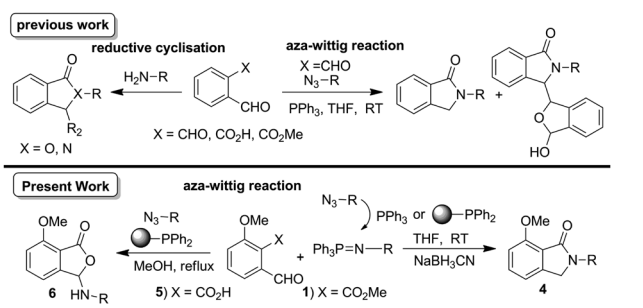
N-Substituted isoindolinone derivatives are heterocyclic compounds with a γ-lactam skeleton that have generated considerable interest due to their varied biological activities; anti-inflammatory,[1] antibacterial,[2] anxiolytic,[3] inhibition of protein–protein interactions[4] and HIV-reverse transcriptase 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 synthesis[14] 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 conditions[13] 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, $NaBH_3CN$ 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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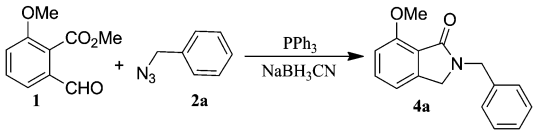
Table 1 Optimisation of aza-Wittig/cyclisation reaction[a]



Entry	Solvent	Temperature	Time[b]	Yield[c] (%)
1	THF	RT	3	75
2	THF	RT	6	90
3	THF	RT	9	81
4	THF	RT	12	85
6	MeCN	RT	6	79
7	EDC	RT	6	72
8	MeOH	RT	6	0

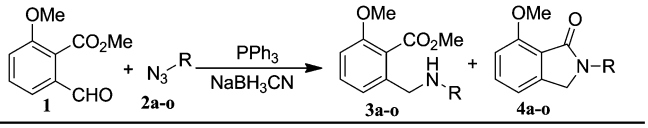
EDC = ethylene dichloride. [a] All the reactions were carried with **1** (0.2 mmol), azide **2a** (0.3 mmol) and PPh_3 (0.4 mmol) in solvent (5.0 mL) and stirred overnight after the addition of $NaBH_3CN$. [b] Reaction time before addition of $NaBH_3CN$. [c] Isolated yields.

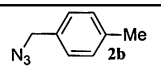
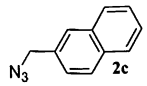
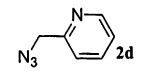
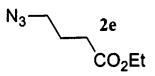
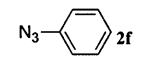
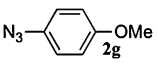
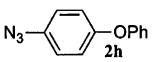
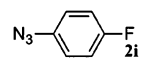
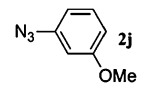
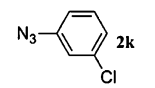
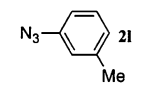
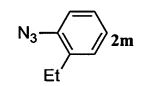
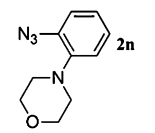
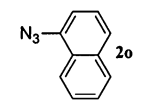
gave the corresponding *N*-isoindolinones **4a–e** exclusively, (ii) phenyl azide **2f**, *p*-substituted aromatic azides **2g**, **i** gave *N*-isoindolinones whereas **2h** gave both isoindolinone **4h** and the amine derivative **3h**, (iii) *m*-substituted aromatic azides **2j–l** resulted in the 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 **2o** 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 $NaBH_3CN$ 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]



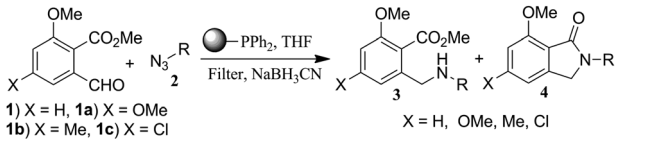
Entry	Azides	Time[b] (h)	Product ratio **3** (%)	Product ratio **4** (%)	Yield[c] (%)
1		12	**3b** (00)	**4b** (100)	72
2		12	**3c** (00)	**4c** (100)	55
3		12	**3d** (00)	**4d** (100)	86
4		12	**3e** (00)	**4e** (100)	69
5		24	**3f** (00)	**4f** (100)	95
6		48	**3g** (00)	**4g** (100)	94
7		48	**3h** (13)	**4h** (64)	77
8		48	**3i** (00)	**4i** (100)	80
9		48	**3j** (32)	**4j** (63)	95
10		48	**3k** (23)	**4k** (69)	92
11		48	**3l** (32)	**4l** (57)	89
12		48	**3m** (100)	**4m** (00)	75
13		48	**3n** (100)	**4n** (00)	55
14		48	**3o** (100)	**4o** (00)	42

[a] All the reactions were stirred at RT for 6 h before the addition of $NaBH_3CN$. [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

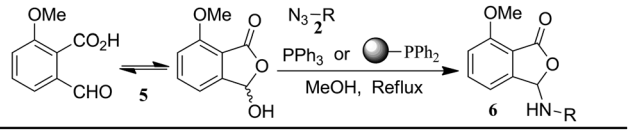
Table 3 Aza-Wittig reactions using polymer-bound triphenylphosphine[a]



Entry	Substrate	Azides	Time[b] (h)	Product ratio 3 (%)	Product ratio 4 (%)	Yield[e] (%)
			18[c]	**3a** (00)	**4a** (100)	76
1	**1**	**2a**	3	**3a** (00)	**4a** (100)	80
			3	**3a** (00)	**4a** (00)	[d]
2	**1**	**2b**	3	**3b** (00)	**4b** (100)	72
3	**1**	**2e**	3	**3e** (00)	**4e** (100)	59
4	**1**	**2g**	24	**3g** (00)	**4g** (100)	79
5	**1**	**2h**	24	**3h** (100)	**4h** (00)	47
6	**1**	**2j**	24	**3j** (100)	**4j** (00)	72
7	**1**	**2k**	24	**3k** (100)	**4k** (00)	64
8	**1a**	**2b**	12	**3ab** (00)	**4ab** (100)	56
9	**1b**	**2b**	12	**3bb** (00)	**4bb** (100)	60
10	**1c**	**2b**	12	**3cb** (00)	**4cb** (100)	68

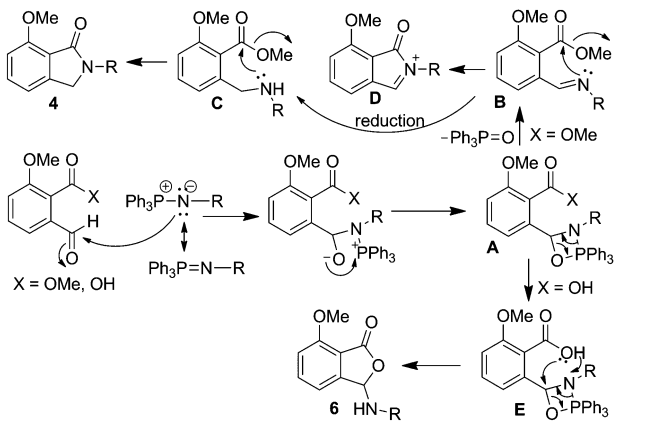
[a] Conditions: **1** (0.1 mmol), azide **2a** (0.2 mmol) and polymer-bound PPh_3 (0.2 mmol) in THF (2.5 mL), RT, 3 h, then filter the resin, added $NaBH_3CN$ (0.2 mmol). [b] Reaction time for cyclisation at reflux temperature. [c] Reaction time for cyclisation at RT. [d] Reaction performed in MeOH at reflux temperature. [e] Isolated yields.

Table 4 Aza-Wittig/cyclisation reaction using *o*-phthalaldehydic acid[a]



Entry	Azides	Product	Solvent	Yield[c] (%)
1	**2a**	**6a**	MeOH	00
2	**2e**	**6e**	MeOH	00
			MeOH[b]	50
3	**2f**	**6f**	MeOH	78
			THF	54
4	**2g**	**6g**	MeOH	66
5	**2j**	**6j**	MeOH	48
6	**2m**	**6m**	MeOH	36

[a] Conditions: **5** (0.15 mmol), azide **2a** (0.3 mmol) and polymer-bound PPh_3 (0.3 mmol), MeOH (5.0 mL), reflux, 5 h. [b] Reaction using PPh_3. [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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