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Novel one-step synthesis of 2-carbonyl/thiocarbonyl isoindolinones and mechanistic disclosure on the rearrangement reaction of *o*-phthalaldehyde with amide/thioamide analogs

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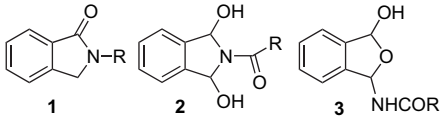
Abstract—A rearrangement reaction of *o*-phthalaldehyde with urea/thiourea analogs or amides/thioamides under the catalysis of TMSCl (trimethylchlorosilane) is described, whereby a series of 2-carbonyl isoindolinones and 2-thiocarbonyl isoindolinones are afforded. This is the first time that the *N*-carbonyl/thiocarbonyl isoindolinones are synthesized in a single step from *o*-phthalaldehyde. Similar reactions using primary amines also proceed smoothly to give corresponding *N*-alkyl or *N*-aryl isoindolinones in this mild catalytic system. The mechanism of this kind of rearrangement is discussed based on new evidences observed from the ESI-MS time-interval monitoring of the full reaction course and deuterium exchange experiments.

1. Introduction

o-Phthalaldehyde is well-known as a versatile reactant due to its special structure of two adjacent substituted formyl groups in the benzene ring.[1] Numerous reactions of *o*-phthalaldehyde have been disclosed both on typical and atypical conversions, and a variety of functional compounds including phthalide,[2a] 1-alkylthioisoindole,[2b,c] isoquinoline,[2d] benzo[*b*]fluorenone,[2e] benzotropone,[2f] etc. have been readily synthesized through the condensation between proper nucleophiles and *o*-phthalaldehyde. Among these reported reactions of *o*-phthalaldehyde, the condensation with ammonia or primary amines was given special attention due to the multifunction of their products—phthalimidines **1** (2,3-dihydro-isoindol-1-ones or isoindolinones, Scheme 1).[3] The isoindolinone skeleton is found in many naturally obtained compounds,[4] and research on the isoindolinone ring system showed that many compounds with this sub-unit exhibit attractive therapeutical activities.[5] What is more, the diverse biological activities[6] of isoindolinones were disclosed during the past decades, and isoindolinones with proper structures could be used as biochemical fluorescent markers as well as precursors of electrically conductive polymers.[7]

As derivatives of isoindolinone, 2-carbonyl isoindolinones and 2-thiocarbonyl isoindolinones **4** also represent great importance in the fields of biochemistry and synthetic study. Primary research showed that compounds containing 2-carbonyl isoindolinone structure could inhibit the proteins poly(ADP-ribose)polymerases (PARPs).[8] Recently, a class of isoindole-fused imidazoles which also contain 2-carbonyl isoindolinone skeleton were reported having special fluorescent properties as well as the ability to stain human squamous epithelium cells.[9] In addition, the 2-carbonyl substituted isoindolinone structure frequently served as an indispensable building block during the total synthesis of some natural products.[10] Furthermore, as substrates or key intermediates, 2-carbonyl isoindolinone compounds were also applied to prepare many other heterocycle-fused compounds.[11] Another significant application of 2-carbonyl isoindolinones is in the dynamic kinetic resolution research.[12] After being substituted in the C-3 position with a hydroxy group, the derivatives, namely *N*-acylhemiaminals obtained as racemic substrates, were able to provide a single enantiomer with excellent stereoselectivity after acylation. The obtained products could then be utilized for further chiral synthesis,[13] whereas identical conversion could not be accomplished with 2-alkyl isoindolinone derivatives **1**.[12a]



Scheme 1. Typical products from the literature reaction of *o*-phthalaldehyde with amines/amides.

Keywords: 2-Carbonyl isoindolinone; 2-Thiocarbonyl isoindolinone; Rearrangement; Mechanism.
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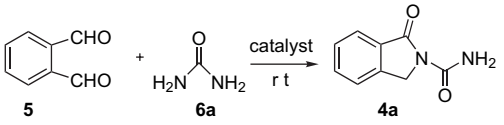
Although primary amines were found to be capable of reacting with *o*-phthalaldehyde to give *N*-alkyl/aryl isoindolinones **1** under different conditions via a rearrangement process,[3] to our best knowledge, neither ureas/thioureas nor amides/thioamides were ever reported to react with *o*-phthalaldehyde following similar rearrangement route to provide corresponding *N*-carbonyl/thiocarbonyl isoindolinones **4** despite the fact that they identically contain the amidocyanogen group(s).[1] Initial studies on the reaction of *o*-phthalaldehyde with amides or urea/thiourea were carried out by Reynolds and co-workers,[14] and DoMinh's group published extended research later.[15] In all these published works, however, the products were just obtained as 2-carbonyl-1,3-dihydroxyisoindole **2** or phthalans **3** or sometimes corresponding dimers,[14c] which were all long viewed as the chemical foundation of a widely used medicinal method of determining urea in blood or serum.[16] No literature has ever declared the products of type **4** whose formation involves a further rearrangement step from those reactions. The current ways of building 2-carbonyl isoindolinones mainly rely on the additional N-acylation of a prepared isoindolinone,[17,8,12] or the utilization of substrates with special structure as well as the catalysis by noble metals[18] or harsh conditions.[11e] Given the desire to develop more practical and diversified methodologies for the synthesis of 2-carbonyl/thiocarbonyl isoindolinones, we report here a convenient, mild, and atom-economical approach for the synthesis of *N*-acyl isoindolinones.

2. Results and discussion

2.1. Optimization of the rearrangement reaction of *o*-phthalaldehyde with urea

This reaction was initially found during our study on the TMSCl catalyzed reactions.[19] When we adopted *o*-phthalaldehyde as one of the substrates, it was found to react exclusively with urea to furnish 1-oxo-1,3-dihydro-isoindole-2-carboxylic acid amide **4a** as the product. Subsequently, in order to achieve the optimal result of this newly found reaction, different conditions were then examined (Table 1). The results showed that this reaction was not solvent-dependent as the product **4a** was formed in good yields both in polar and nonpolar solvents (entries 1–3). It is noteworthy that this reaction was found to take place efficiently in the ionic liquid [bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate), and the product could be easily isolated through extraction with ethyl acetate, the reactions with urea/thiourea derivatives also proceeded smoothly in [bmim]BF_4. Unfortunately, when amides were subjected to the reaction in place of ureas, poor results were observed, which impelled us to further explore other effects in our previously adopted CH_3CN/DMF system. We used different Lewis and Bronsted acids as catalysts (entries 6–9), and the results showed that the catalysis of TMSCl was crucial to this reaction: the optimal catalytic amount of TMSCl was finally established as 0.8 equiv mol (entries 5 and 11).

Table 1. Optimization of the reaction conditions using *o*-phthalaldehyde and urea[a]



5 6a 4a

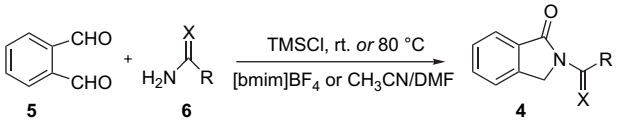
Entry	Solvent(s)	Catalyst	Yield[b] (%)
1	CH_3CN	TMSCl	Messy[b]
2	DMF	TMSCl	81
3	Benzene	TMSCl	76
4	[bmim]BF_4	TMSCl	85
5	CH_3CN/DMF[c]	TMSCl	87
6	CH_3CN/DMF	None	0
7	CH_3CN/DMF	HCl[d]	25
8	CH_3CN/DMF	$AlCl_3$	0
9	CH_3CN/DMF	$InCl_3$	Trace
10	CH_3CN/DMF	$TiCl_4$	Trace
11[e]	CH_3CN/DMF	TMSCl	85

[a] Unless otherwise specified, the general reaction conditions are **5** (1 mmol), **6a** (1 mmol) mixed and stirred for 7 h in 1.5 mL solvent(s) in the presence of 0.8 mmol catalyst.
[b] Isolated yields.
[c] $V_{CH_3CN}/V_{DMF} = 2:1$.
[d] Concentrated hydrochloric acid: 37%.
[e] TMSCl: 1.6 mmol for testing the effect of catalyst's amount.

2.2. Rearrangement reaction of *o*-phthalaldehyde with different ureas/thioureas/amides/thioamides

To examine the practical scope of the reaction, a class of *N*-substituted ureas and thioureas were then subjected to the reactions (Table 2). These reactions were carried out in the aforementioned ionic liquid system (substrates **6a–f**). The result was that corresponding products were obtained

Table 2. Reactions of different urea/thiourea and amide/thioamide analogs with *o*-phthalaldehyde[a]

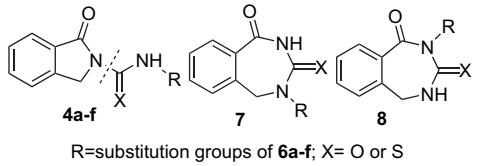


5 6 4

Substrate	R	X	Product	Yield[b] (%)
6a[c]	NH_2	O	**4a**	85
6b	$NHCH_3$	O	**4b**	83
6c	NHC_2H_5	O	**4c**	88
6d	NHPh	O	**4d**	76
6e	$NHCH_3$	S	**4e**	75
6f	$NHCH_2CH{=}CH_2$	S	**4f**	67
6g	CH_3	S	**4g**	70
6h	H	O	**4h**	81
6i	CH_3	O	**4i**	86
6j	CH_2Cl	O	**4j**	73
6k	CH_2CN	O	**4k**	67
6l	$(CH_2)_4CH_3$	O	**4l**	90
6m	$CH(CH_3)_2$	O	**4m**	83
6n	$CH{=}CH_2$	O	**4n**	78
6o	CH_2Ph	O	**4o**	75
6p[d]	Ph	O	**4p**	87
6q	4-FPh	O	**4q**	86
6r	2,3-$(CH_3)_2$Ph	O	**4r**	88
6s	3,5-$(OCH_3)_2$Ph	O	**4s**	90
6t[e]	NH_2	S	—	—

[a] Unless otherwise specified, the general conditions are **5** (1 mmol), **6** (1 mmol), TMSCl (0.8 mmol) mixed with 1.5 mL 2:1 CH_3CN/DMF under corresponding temperature and stirred for 7–12 h.
[b] Isolated yields.
[c] For substrates **6a–f**, the ionic liquid [bmim]BF_4 was used as medium.
[d] For substrates **6p–s**, a reflux temperature is necessary for satisfactory results, while all other reactions were observed under room temperature.
[e] No target product was observed.

in good yields. Furthermore, in order to clearly characterize the products **4a–f**, the ESI-MS^2 fragmentation experiments were applied besides the conventional ^{1}H, ^{13}C NMR, and HRMS analyses since there may exist possible isomers **7** or **8** that could not be excluded by the ^{1}H and ^{13}C NMR spectra (Scheme 2). Main fragmentations (ESI-MS^2 fragmentation spectra are available in Supplementary data) of these compounds were then found to follow the general route displayed in Scheme 2 (the broken line in **4a–f**), from which we could confirm the structure of products as **4a–f**. The X-ray crystal diffraction of **4c** (Fig. 1) provided further evidence for this conclusion.[20] Meanwhile, the failure of the reaction with thiourea was somewhat unexpected. It merely led to a messy mixture without the target product (TLC and ESI) despite our effort. Notwithstanding this, an *N*-substituted electron-donating group promoted the reaction of thiourea (**6e–f**).



Scheme 2. Structure and main ESI-MS^2 fragmention of **4a–f** as well as possible isomers.

The results achieved from substrates **6a–f** prompted us to further investigate the reactions using amides/thioamides as substitution of ureas/thioureas. As mentioned above, when the amides were subjected to the ionic liquid [bmim]BF_4 for similar reaction, poor results were observed, which directed us back to the protocol of CH_3CN/DMF system. First, a class of aliphatic amides were used as substrates; as expected, corresponding 2-carbonyl/thiocarbonyl isoindolinones were obtained in good to excellent yields under room temperature (**6g–o**). In continuation of these experimental results, we further investigated the reactions with aromatic amides instead of aliphatic ones since previous work had claimed that the steric effect of aromatic amides gave different results from those of aliphatic amides.[15a] To our delight, several benzamides tested all selectively led to corresponding 2-carbonyl isoindolinones as the main products (**6p–s**) without unexpected exception. What was different was that the reactions of (substituted) benzamides required refluxing temperature in order to achieve satisfactory yields. This discrepancy may be ascribed to the steric effect.

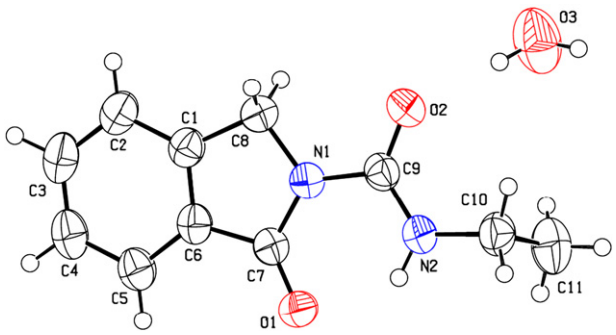
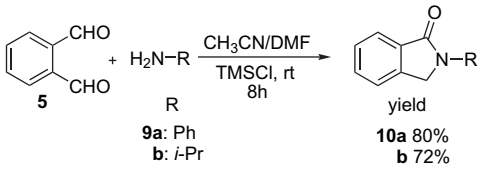


Figure 1. X-ray crystal structure of **4c**.

To broaden the scope of this TMSCl catalyzed system, we turned our attention to the reactions between primary amines and *o*-phthalaldehyde. Since reactions of this kind were widely studied for their values both in synthetic and medicinal researches, it was our goal as well to achieve this conversion using this newly developed methodology and thereby provide a general guideline for both the preparation of 2-carbonyl/thiocarbonyl and 2-alkyl/aryl isoindolinones. The easily available reagents phenylamine and isopropylamine were selected as representatives of arylamine and alkylamine, respectively, and both substrates proceeded well to the anticipated products in good yields (Scheme 3).



Scheme 3. Reactions of *o*-phthalaldehyde with primary amines.

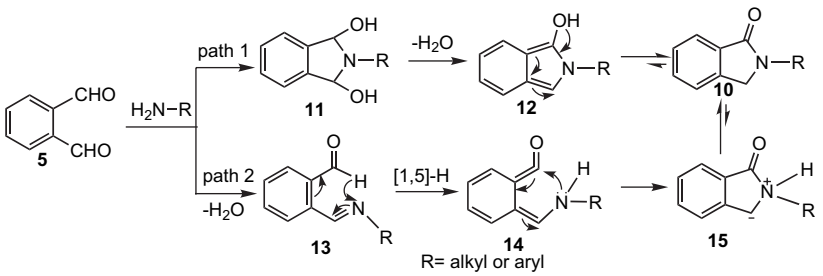
All products **4a–s**, **10a** and **b** were characterized with ^{1}H and ^{13}C NMR, HRMS, ESI-MS, and IR analyses, additional characterizations of **4a–f** were carried out as previously described. Products **4b–e**, **4h**, **4j–o** as well as **4q–s** were obtained as new compounds.

2.3. Mechanistic study and discussion

Our studies on the mechanism of these reactions were designed on the basis of related mechanistic research on previously developed reactions of primary amines with *o*-phthalaldehyde. According to currently available publications,[21] the main controversies about this rearrangement focus on the intermediates formed during the reaction process. Intermediate **11** (Scheme 4, path 1) was regarded as the key structure for the formation of the products in the classical proposal, while Alajarín and co-workers recently proposed a [1,5]-*H* sigmatropic rearrangement route based on computational study as well as correlative literature in which the intermediate **13** was believed to play crucial role in providing the final products (Scheme 4, path 2).[21]

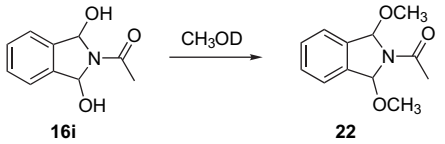
In our experiments, however, amides/thioamides (or ureas/thioureas) substituted primary amines, which made us believe that similar intermediates (Scheme 5) **16** and **21** (R=CH_3, X=O) have the stability to be detected by ESI-MS if formed during the reaction course. Thus, we selected the reaction of acetamide with *o*-phthalaldehyde as the model to monitor the intermediates with ESI-MS during the reaction process with a time-interval of 15 min. To our delight, the existence of **16** (R=CH_3, X=O, see Supplementary data for details) was successfully detected[22] during the reaction, and the ESI-MS signal disappeared following completion of the reaction. On the other hand, characteristic fragmentation signals supporting intermediate **21** were not observed under the same condition (path 2a).

Afterward, we deliberately applied a deuterium reagent CH_3OD as commutative reagent in order to probe the exact route of the rearrangement. When CH_3OD was added as



Scheme 4.

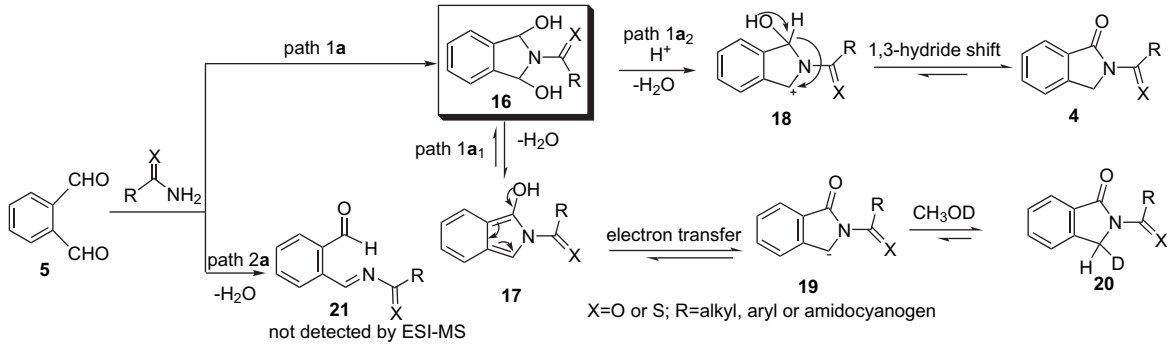
extra additive to the typical reaction system, the deuterium substituted product **20** was obtained in 28.57% yield based on the HRMS analysis, further characterization of ESI-MS^2 fragmentation (Fig. 2) and ^1H as well as ^{13}C NMR (see Supplementary data) confirmed the structure of **20**. It is interesting that when CH_3OD was used as the single solvent for the same reaction, the formation of both **4i** and **20** was remarkably prevented (TLC and ESI-MS), instead, characteristic signals matching the alternative product **22** (Scheme 6) were observed in ESI-MS.[23] Moreover, the reaction outlined in Scheme 6 supported **16** as the main intermediates. Therefore, we reasonably proposed path 1a (Scheme 5) as the general mechanism of this rearrangement condensation. Consequently, the obtained deuterium substituted product **20** revealed that the electron transfer (path $1a_1$) which led to an intermediate **19** was the main cause which led to the rearranged products in our experiments, while the other proposed route path $1a_2$ is not favored based on our experiment. Further investigation on this topic is currently in progress in our group.



Scheme 6.

3. Conclusion

We developed a new type of TMSCl catalyzed reaction of *o*-phthalaldehyde with acylamide/thioamide or urea/thiourea compounds, in which 2-carbonyl/thiocarbonyl isoindolinones were readily formed through a rearrangement process. This marks the first time that this conversion is reported. The said catalytic system developed was proven to have general compatibility and efficiency both with the reaction of newly found amides/thioamides and those of the previously reported primary amines. In addition, as mechanisms of this kind are presently controversial, new evidences based on the ESI-MS combined with deuterium exchange experiments were provided to describe the course of the rearrangement.



Scheme 5. Mechanistic display of TMSCl catalyzed rearrangement reactions of *o*-phthalaldehyde with carbonyl/thiocarbonyl substrates.

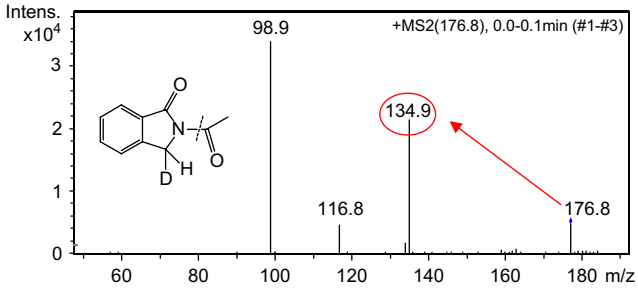


Figure 2. ESI-MS fragmentation of deuterium substituted product **20**.

4. Experimental

4.1. General

All chemicals were obtained from commercial suppliers and used without further purification. Anhydrous conditions

are not required for the reaction. Melting points were determined using XT-4 apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE DMX-500 spectrometer at 500 MHz and 125 MHz in $CDCl_3$, respectively. Chemical shifts are reported in parts per million (δ), relative to the internal standard of tetramethylsilane (TMS). ^{1}H and ^{13}C NMR spectra were acquired under standard conditions (5 mm QNP probe). Mass spectra were performed on a Bruker Esquire 3000plus mass spectrometer (Bruker–Franzen Analytik GmbH Breman, Germany) equipped with ESI interface and ion trap analyzer. HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source (Billelica, MA, USA).

4.2. General procedure for the TMSCl catalyzed reactions between ureas/thioureas and *o*-phthalaldehyde

o-Phthalaldehyde (1 mmol) and ureas/thioureas (1 mmol) were placed in a flame-dried round-bottomed flask, 1.5 mL of ionic liquid [bmim]BF_4 was used as reaction medium, 0.8 mmol TMSCl was added, and the mixture was stirred for 7–9 h at room temperature. The completion of reactions was determined by TLC. The mixture was extracted with (3×10 mL) acetate ester. The combined organic layer was evaporated in vacuum, and the residue was obtained as analytically pure product. An additional recrystallization with ethanol was carried out when necessary. Compound **4f** was isolated by silica gel chromatography with the elution of mixed ethyl acetate and petroleum ether (V_{EA}/V_{PE}=1:3).

4.2.1. 1-Oxo-1,3-dihydro-isoindole-2-carboxylic acid amide (4a). Colorless crystals, mp: 191–193 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (1H, s), 7.66–7.82 (3H, m), 7.60 (1H, s), 7.54–7.57 (1H, m), 4.78 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 153.4, 141.3, 134.0, 131.0, 128.7, 125.0, 123.5, 48.4; IR (KBr, cm^{-1}): 3371, 3228, 2917, 1739, 1719, 1670, 1586, 1473, 750; HRMS: calcd for $C_9H_8N_2O_2Na$ (M+Na)$^+$: 199.0478; found: 199.0476.

4.2.2. 1-Oxo-1,3-dihydro-isoindole-2-carboxylic acid methylamide (4b). Yellow crystals, mp: 153–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (1H, s), 7.50–7.89 (4H, m), 4.84 (2H, s), 2.98 (3H, d, J=5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 153.8, 141.4, 133.8, 131.4, 128.7, 124.9, 123.5, 48.8, 26.7; IR (KBr, cm^{-1}): 3317, 2942, 2865, 1704, 1682, 1583, 1551, 1469, 749; HRMS: calcd for $C_{10}H_{10}N_2O_2Na$ (M+Na)$^+$: 213.0643; found: 213.0628.

4.2.3. 1-Oxo-1,3-dihydro-isoindole-2-carboxylic acid ethylamide (4c). Colorless crystals, mp: 108–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (1H, s), 7.52–7.90 (4H, m), 4.86 (2H, s), 3.45 (2H, q, $J_{1,2}$=7.0 Hz, $J_{3,2}$=6.2 Hz), 1.26 (3H, t, $J_{2,1}$=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 153.2, 141.4, 133.8, 131.6, 128.7, 124.9, 123.6, 48.8, 35.1, 15.3; IR (KBr, cm^{-1}): 3325, 2968, 2930, 2872, 1716, 1677, 1603, 1540, 1467, 731; HRMS: calcd for $C_{11}H_{12}N_2O_2Na$ (M+Na)$^+$: 227.0791; found: 227.0784.

4.2.4. 1-Oxo-1,3-dihydro-isoindole-2-carboxylic acid phenylamide (4d). Colorless crystals, mp: 181–183 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.68 (1H, s), 7.05–7.88 (9H, m), 4.86 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 150.5, 141.3, 137.7, 134.2, 131.2, 129.3, 128.9, 125.1, 124.3, 123.6, 120.3, 48.8; IR (KBr, cm^{-1}): 3448, 2931, 1711, 1604, 1559, 1498, 1441, 738; HRMS: calcd for $C_{15}H_{12}N_2O_2Na$ (M+Na)$^+$: 275.0791; found: 275.0785.

4.2.5. 1-Oxo-1,3-dihydro-isoindole-2-carbothioic acid methylamide (4e). Yellow crystals, mp: 139–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.83 (1H, s), 7.47–8.02 (4H, m), 5.54 (2H, s), 3.26 (3H, d, J=4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.8, 181.5, 141.1, 139.1, 133.8, 129.0, 126.7, 122.1, 61.7, 32.5; IR (KBr, cm^{-1}): 3210, 2964, 1710, 1666, 1591, 1557, 1477, 1464, 736; HRMS: calcd for $C_{10}H_{10}N_2OSNa$ (M+Na)$^+$: 229.0406; found: 229.0404.

4.2.6. 1-Oxo-1,3-dihydro-isoindole-2-carbothioic acid allylamide (4f). Yellow crystals, mp: 134–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.02 (1H, s), 7.51–8.07 (4H, m), 5.98–6.04 (1H, m), 5.58 (2H, s), 5.43 (1H, d, J=16.5 Hz), 5.28 (1H, J=11.5 Hz), 4.44 (2H, t, $J_{1,2}$=4.5 Hz, $J_{3,2}$=5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 180.7, 141.3, 139.2, 133.9, 132.0, 129.1, 126.8, 122.2, 118.1, 61.9, 49.0; IR (KBr, cm^{-1}): 3282, 2913, 1710, 1619, 1533, 1469, 1427, 986, 920, 734; HRMS: calcd for $C_{12}H_{12}N_2OSNa$ (M+Na)$^+$: 255.0563; found: 255.0562.

4.3. Typical procedure for TMSCl catalyzed reactions of *o*-phthalaldehyde and aliphatic amides

Reactions in this section were performed under the same general conditions as those of the reaction of ureas/thioureas, but the mixed solvents of CH_3CN/DMF ($V_{CH_3CN}/V_{DMF}=2:1$) were used as media in place of ionic liquid and stirred for 10–12 h for completion of reactions. The isolation of products was generally accomplished by silica gel column chromatography with elution of mixed ethyl acetate and petroleum ether (V_{EA}/V_{PE}=1:3).

4.3.1. 2-Thioacetyl-2,3-dihydro-isoindol-1-one (4g). Brown crystals, mp: 168–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50–8.11 (4H, m), 5.08 (2H, s), 2.98 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.0, 172.5, 141.4, 139.1, 133.8, 129.0, 127.1, 122.6, 55.7, 28.1; IR (KBr, cm^{-1}): 2926, 1698, 1603, 1423, 724; HRMS: calcd for $C_{10}H_9NOSNa$ (M+Na)$^+$: 214.0295; found: 214.0297.

4.3.2. 1-Oxo-1,3-dihydro-isoindole-2-carbaldehyde (4h). Colorless crystals, mp: 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (1H, s), 7.51–7.94 (4H, m), 4.73 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 160.3, 142.2, 134.9, 130.2, 129.1, 125.4, 124.0, 45.7; IR (KBr, cm^{-1}): 2921, 1731, 1697, 1613, 1469, 1438, 737; HRMS: calcd for $C_9H_7NO_2Na$ (M+Na)$^+$: 184.0369; found: 184.0368.

4.3.3. 2-Acetyl-2,3-dihydro-isoindol-1-one (4i). Colorless crystals, mp: 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–7.92 (4H, m), 4.81 (2H, s), 2.68 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 168.0, 141.3, 134.3, 131.5, 128.9, 125.4, 123.7, 48.3, 25.0; IR (KBr, cm^{-1}): 2934, 2860, 1731, 1686, 1612, 1472, 1431, 1381, 744; HRMS: calcd for $C_{10}H_9NO_2Na$ (M+Na)$^+$: 198.0525; found: 198.0521.

4.3.4. 2-(2-Chloro-acetyl)-2,3-dihydro-isoindol-1-one (4j). To obtain this product, the rest of the components and catalyst must be mixed and stirred under room temperature for 5 min before adding the substrate 2-chloro-acetamide. Yellow crystals, mp: 135–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54–7.94 (4H, m), 4.91 (2H, s), 4.88 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 167.2, 141.7, 134.8, 131.5, 129.1, 125.7, 123.8, 48.6, 45.2; IR (KBr, cm^{-1}): 2955, 1721, 1613, 1464, 1450, 1403, 744; HRMS: calcd for $C_{10}H_8ClNO_2Na$ $(M+Na)^+$: 232.0136; found: 232.0134.

4.3.5. 3-Oxo-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionitrile (4k). Colorless crystals, mp: 214–216 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–8.00 (4H, m), 4.90 (2H, s), 4.31 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 162.6, 141.4, 135.3, 130.2, 129.4, 125.9, 123.9, 113.5, 48.6, 28.4; IR (KBr, cm^{-1}): 2959, 2252, 1731, 1704, 1614, 1464, 1453, 1382, 741; HRMS: calcd for $C_{11}H_8N_2O_2Na$ $(M+Na)^+$: 223.0478; found: 223.0476.

4.3.6. 2-Hexanoyl-2,3-dihydro-isoindol-1-one (4l). Colorless crystals, mp: 79–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50–7.92 (4H, m), 4.82 (2H, s), 3.10 (2H, t, J=7.5 Hz), 1.73–7.76 (2H, m, J=7.5 Hz), 1.38–1.42 (4H, m), 0.92 (3H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7, 167.8, 141.4, 134.2, 131.7, 128.8, 125.4, 123.6, 48.4, 37.1, 31.6, 24.3, 22.7, 14.2; IR (KBr, cm^{-1}): 2954, 2929, 2848, 1713, 1695, 1615, 1467, 1440, 740; HRMS: calcd for $C_{14}H_{17}NO_2Na$ $(M+Na)^+$: 254.1151; found: 254.1145.

4.3.7. 2-Isobutyryl-2,3-dihydro-isoindol-1-one (4m). Colorless crystals, mp: 84–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48–7.91 (4H, m), 4.81 (2H, s), 3.95 (1H, m), 1.25 (6H, d, J=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.8, 167.5, 141.4, 134.2, 131.7, 128.8, 125.4, 123.6, 48.8, 34.2, 19.0; IR (KBr, cm^{-1}): 2981, 2963, 2935, 2870, 1716, 1696, 1611, 1467, 1446, 1388, 734; HRMS: calcd for $C_{12}H_{13}NO_2Na$ $(M+Na)^+$: 226.0838; found: 226.0834.

4.3.8. 2-Acryloyl-2,3-dihydro-isoindol-1-one (4n). White solid, mp: 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–7.93 (5H, m), 6.62–6.66 (1H, m), 5.95–5.97 (1H, m), 4.90 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 166.2, 141.6, 134.4, 131.6, 131.4, 130.0, 128.9, 125.6, 123.7, 48.6; IR (KBr, cm^{-1}): 2918, 2852, 1732, 1672, 1614, 1473, 1446, 1411, 896, 735; HRMS: calcd for $C_{11}H_9NO_2Na$ $(M+Na)^+$: 210.0525; found: 210.0520.

4.3.9. 2-Phenylacetyl-2,3-dihydro-isoindol-1-one (4o). Colorless crystals, mp: 139–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20–7.88 (9H, m), 4.78 (2H, s), 4.42 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 167.8, 141.5, 134.4, 131.6, 130.0, 128.9, 128.8, 127.3, 125.6, 123.7, 48.7, 43.1; IR (KBr, cm^{-1}): 2923, 2851, 1719, 1705, 1619, 1498, 1462, 1446, 735; HRMS: calcd for $C_{16}H_{13}NO_2Na$ $(M+Na)^+$: 274.0838; found: 274.0835.

4.4. Representative procedure for the TMSCl catalyzed reactions of *o*-phthalaldehyde and benzamides

Identical conditions adopted as in the above aliphatic amides' reactions caused ideal results in this section, but a reflux temperature was required for all benzamide reactions carried out in our laboratory.

4.4.1. 2-Benzoyl-2,3-dihydro-isoindol-1-one (4p). Colorless crystals, mp: 137–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.88 (9H, m), 5.05 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 167.1, 141.6, 134.7, 134.4, 132.0, 131.3, 129.0, 128.9, 128.0, 125.5, 123.7, 49.0; IR (KBr, cm^{-1}): 2946, 1732, 1671, 1616, 1599, 1496, 1470, 1441, 733; HRMS: calcd for $C_{15}H_{11}NO_2Na$ $(M+Na)^+$: 260.0682; found: 260.0675.

4.4.2. 2-(4-Fluoro-benzoyl)-2,3-dihydro-isoindol-1-one (4q). Colorless crystals, mp: 148–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13–7.90 (8H, m), 5.06 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 167.2, 141.6, 134.5, 131.9, 131.8, 131.2, 129.0, 125.6, 123.7, 115.3, 115.1, 49.1; IR (KBr, cm^{-1}): 2947, 1719, 1671, 1603, 1509, 1448, 737; HRMS: calcd for $C_{15}H_{10}FNO_2Na$ $(M+Na)^+$: 278.0588; found: 278.0581.

4.4.3. 2-(2,3-Dimethyl-benzoyl)-2,3-dihydro-isoindol-1-one (4r). Colorless crystals, mp: 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.84 (4H, m), 7.12–7.29 (3H, m), 5.05 (2H, s), 2.34 (3H, s), 2.24 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 166.6, 141.5, 137.4, 136.6, 134.5, 133.2, 131.5, 131.3, 129.0, 125.7, 125.6, 124.1, 123.8, 48.5, 20.3, 16.6; IR (KBr, cm^{-1}): 2955, 2860, 1749, 1672, 1615, 1493, 1468, 1441, 1375, 743; HRMS: calcd for $C_{17}H_{15}NO_2Na$ $(M+Na)^+$: 288.0995; found: 288.0986.

4.4.4. 2-(3,5-Dimethoxy-benzoyl)-2,3-dihydro-isoindol-1-one (4s). White solid, mp: 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–7.89 (4H, m), 6.64 (1H, t), 6.81 (2H, d), 5.04 (2H, s), 3.83 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 166.9, 160.5, 141.6, 136.6, 134.4, 131.3, 129.0, 125.7, 123.7, 106.7, 104.3, 55.8, 49.1; IR (KBr, cm^{-1}): 2972, 2947, 2847, 1749, 1671, 1604, 1496, 1454, 1426, 1372, 1293, 746; HRMS: calcd for $C_{17}H_{15}NO_4Na$ $(M+Na)^+$: 320.0893; found: 320.0883.

4.5. Preparation of 10a and 10b

The preparation process followed the general conditions for **4f–o**.

4.5.1. 2-Phenyl-2,3-dihydro-isoindol-1-one (10a). Colorless crystals, mp: 164–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16–7.93 (9H, m), 4.83 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 140.3, 139.7, 133.4, 132.2, 129.3, 128.5, 124.6, 124.3, 122.8, 120.0, 50.9; IR (KBr, cm^{-1}): 3026, 2922, 2851, 1686, 1595, 1501, 1465, 1440, 732; HRMS: calcd for $C_{14}H_{11}NONa$ $(M+Na)^+$: 232.0733; found: 232.0726.

4.5.2. 2-Isopropyl-2,3-dihydro-isoindol-1-one (10b). Colorless crystals, mp: 82–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.83 (4H, m), 4.67 (1H, m, $J_{1,2}$=7 Hz), 4.33 (2H, s), 1.28 (6H, d, $J_{2,1}$=7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 141.4, 133.6, 131.2, 128.1, 123.4, 122.9, 45.2, 42.8, 21.0; IR (KBr, cm^{-1}): 2975, 2929, 2864, 1672, 1591, 1471, 1461, 1411, 1386, 740; HRMS: calcd for $C_{11}H_{13}NONa$ $(M+Na)^+$: 198.0889; found: 198.0884.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.009.

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20. Crystallographic data (excluding structure factors) for the structure of **4c** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 646780. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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22. The exact structure was established through the in situ fragmentation of ESI-MS^2 in contrast to fragmentation of standard compound, which was prepared following literature route in Ref. 14c.
23. The product **22** was primarily proposed according to the corresponding ESI-MS signals $[M+H]^+$, $[M+Na]^+$, $[2M+Na]^+$ observed in ESI-MS, isolation of pure compound wasn't successful due to the instability of **22**.