



## Studying the reactivity of (phthalazin-1(2*H*)-on-2-yl)methyl trichloroacetimidate towards different C- and O-nucleophiles

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### ABSTRACT

A simple and efficient synthesis of phthalazin-1(2*H*)-one 2-substituted derivatives is achieved in very good yields via reaction of a phthalazinone–trichloroacetimidate with various C- and O-nucleophiles such as aromatic, heteroaromatic and olefinic reagents, sugars and cholesterol in CH<sub>2</sub>Cl<sub>2</sub> in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf).

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The synthesis of new compounds and testing their biological and pharmacological activities are the major goals of drug development projects. Nitrogen-containing heterocyclic compounds have received much attention as shown by the numerous studies published on their applicability in different areas, especially as drugs.<sup>1,2</sup> Phthalazines are examples of nitrogen heterocycles that possess exciting biological properties.<sup>3–5</sup> They form the structural profile for several biologically active compounds and hence they are considered as important key elements. Several reports in the literature have focused on the pharmacology of phthalazine derivatives. These reports have resulted in a great number of contributions in diverse areas of interest.<sup>6–11</sup> Phthalazines have been reported to possess anticonvulsant,<sup>12</sup> cardiotonic<sup>13</sup> and vasorelaxant activities.<sup>14,15</sup> Additionally, phthalazines have recently been reported to potentially inhibit serotonin reuptake and are considered as anti-depression agents.<sup>16</sup>

As a part of our ongoing research on drug discovery, we needed to develop a facile and rapid synthetic pathway to new drug-like small organic molecules containing the phthalazinone moiety. Our research in this area has resulted in the synthesis of a series of indole–pyrimidine (meridianin D analogues) and phthalazinone–amino acid conjugates. These conjugates were tested as anti-

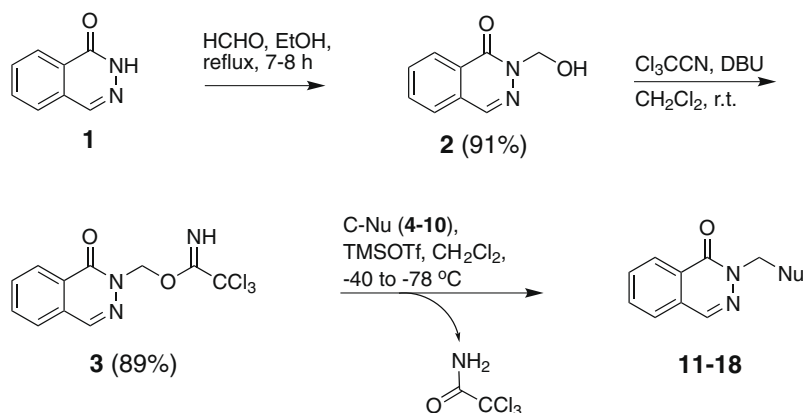
tumour agents and showed moderate activities against the Caucasian breast adenocarcinoma MCF7 cell line.<sup>17,18</sup>

Several approaches have been reported in the literature for the synthesis of phthalazinones.<sup>12,19</sup> Generally, phthalazines are synthesized from either phthalic anhydride derivatives, 2-aryl-3-hydroxyinden-1-ones, or  $\beta$ -diketones via condensation with hydrazine hydrate by either heating<sup>20</sup> or applying microwave irradiation.<sup>15</sup> However, these routes could not be used for the introduction of *N*-methylenyl substitution. Trichloroacetimidate has been shown to be a good leaving group leading to C–O bond formation and is used extensively in carbohydrate research.<sup>21</sup> Recently, new methodologies have been developed for C–C bond formation via reaction of trichloroacetimidate derivatives with C-nucleophiles in the presence of Lewis acids.<sup>22,23</sup> This inspired us to investigate the addition of a methylenyl moiety at the *N*-2 position of phthalazinone using the trichloroacetimidate approach.

In this Letter, we present an efficient procedure for the synthesis of *N*-substituted phthalazinones. Starting with phthalazin-1(2*H*)-one (**1**), we synthesized the corresponding trichloroacetimidate **3** as a key product. This compound was subsequently reacted with a variety of C- and O-nucleophiles in the presence of TMSOTf to produce a series of new phthalazinone derivatives.

Thus, commercially available phthalazin-1(2*H*)-one (**1**) was initially transformed into 2-(hydroxymethyl)phthalazin-1(2*H*)-one (**2**)<sup>24</sup> via reaction with formaldehyde in ethanol at reflux. The trichloroacetimidate **3**<sup>25</sup> was synthesized by reacting **2** with

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**Scheme 1.** The reaction of phthalazinone trichloroacetimidate with C-nucleophiles.

trichloroacetonitrile in dry dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1). The reaction ran smoothly at room temperature and was terminated after complete consumption of the starting materials as indicated by TLC. Trichloroacetimidate **3** was further reacted with electron-rich aromatic C-nucleophiles **4–10**<sup>26</sup> in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst to afford the corresponding adducts **11–18** in high yields (Table 1).

As fluorobenzene (**4**) has two equivalent *o*- and one *p*-position susceptible to attack, two inseparable regioisomers were obtained which were assigned as the *o*- and the *p*-products **11a** and **11b**. The <sup>1</sup>H NMR spectrum showed two singlets at 5.74 and 5.71 ppm for the CH<sub>2</sub>-linker protons in a ratio of 3:2. The singlet at 5.74 ppm was assigned to the *o*-regioisomer and the singlet at 5.71 ppm to the *p*-regioisomer. 1-Bromo-2,4-dimethoxybenzene (**5**) has two equivalent nucleophilic sites (C-3 and C-5) and accordingly, two products **12** and **13** were obtained, in comparable 40% and 47% yields. The <sup>1</sup>H NMR spectra of **12** and **13** allowed differentiation between the two regioisomers. Compound **12** showed two doublets assigned to the two neighbouring aromatic protons at 6.59 (d, *J* = 8.9 Hz) and 7.45 (d, *J* = 8.9 Hz) ppm, while **13** showed two singlets at 6.48 and 7.29 ppm assigned to the two separate aromatic protons. Anisole (**6**) has two equivalent *o*- and one *p*-position which are possible nucleophilic sites. Reaction of **6** gave inseparable regioisomers **14a** and **14b** in an isomeric ratio of 2:1 (*o/p*-isomeric ratio) as determined by <sup>1</sup>H NMR spectroscopy. Although TLC of the reaction mixture of 1,3-dimethoxybenzene (**7**) with **3** showed two spots, only one major product **15**<sup>27</sup> was isolated.

Silylated reagents have also proved to effect C–C bond formation.<sup>22,28,29</sup> Thus, trichloroacetimidate **3** was reacted with different silylated reagents including, 1-phenyltrimethylsiloxyethene (**8**), 3-trimethylsilylprop-1-ene (**9**) and trimethyl(vinyl)silane (**10**) in the presence of TMSOTf to give, respectively, products **16**, **17** and **18** (Table 1). These compounds were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopies. The mechanism of the nucleophilic substitution reaction of trichloroacetimidate with C- and O-nucleophiles has been studied previously.<sup>30</sup> In all cases, trichloroacetamide was obtained as a by-product.

Next, we directed our attention towards the reaction of **3** with several O-nucleophiles under the conditions reported above (Scheme 2). Amongst the O-nucleophiles that were tested, reactivity towards trichloroacetimidate decreased for primary, secondary and aromatic hydroxy groups. Reactions between **3** and primary alcohols such as **19** and **20** afforded readily the corresponding ethers **27**<sup>31</sup> and **28**<sup>32</sup> in high yields (Table 2). Another primary alcohol, *N*-hydroxymethylphthalimide (**21**), similarly underwent etherification on reaction with **3** to afford **29**. Analogously, the secondary alcohol 2-allyl-3-hydroxyisoindolin-1-one (**22**) reacted

with **3** to afford a mixture of two inseparable stereoisomers **30a** and **30b** in a 1:1 ratio as determined by <sup>1</sup>H NMR spectroscopy.

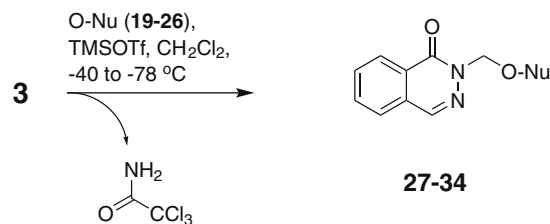
**Table 1**  
Reaction of C-nucleophiles **4–10** with trichloroacetimidate **3**

Entry	C-Nucleophile	Product	Yield % (Ratio)
1			89 (3:2)
	<b>4</b>		
2			41
	<b>5</b>		47
3			90 (2:1)
	<b>6</b>		
4			89
	<b>7</b>		

(continued on next page)

**Table 1** (continued)

Entry	C-Nucleophile	Product	Yield % (Ratio)
5			89
6			90
7			86

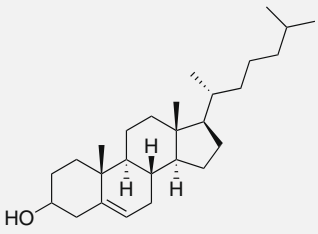
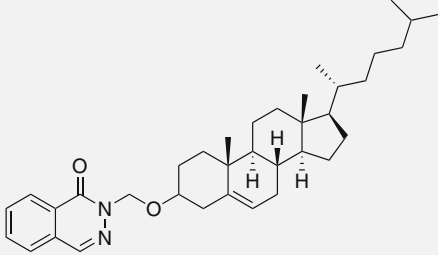
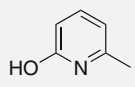
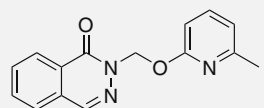
**Scheme 2.** The reaction of phthalazinone trichloroacetimidate with O-nucleophiles.

Etherification of secondary alcohols **23** and **24** was successfully performed under similar conditions to afford the  $\alpha$ -anomer of the ether **31** (5.44 ppm, s, 1H, H-1) and an inseparable mixture of the  $\alpha$ - and  $\beta$ -anomers of **32** (4.75–4.98 ppm, m, 1H, H-1), respectively, in good yields. It was noticed that the dimethoxytrityl group (DMT) of **23** was cleaved during the reaction. Similarly, cholesterol (**25**) reacted with **3** to afford **33** in 84% yield. The reaction between trichloroacetimidate **3** and the hydroxy group of heteroaromatic system **26** gave **34** in high yield. The structures of products **27–34** were confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopies.

**Table 2**  
Reaction of O-nucleophiles **19–26** with trichloroacetimidate **3**

Entry	O-Nucleophile	Product	Yield %
1			90
2			88
3			89
4			86
5			75
6			86

Table 2 (continued)

Entry	O-Nucleophile	Product	Yield %
7			84
8			90

In conclusion, a facile and efficient method for the preparation of novel 1-*N*-phthalazin-1(2*H*)-one derivatives is reported via reactions of a phthalazine–trichloroacetimidate derivative with various aromatic, heteroaromatic and olefinic reagents, sugars and cholesterol in  $\text{CH}_2\text{Cl}_2$  in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf).

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.09.068](https://doi.org/10.1016/j.tetlet.2009.09.068).

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- Synthesis of 2-(hydroxymethyl)phthalazin-1(2*H*)-one (**2**). To a solution of phthalazin-1(2*H*)-one (5.0 g, 34.2 mmol) in dry ethanol (30 mL) was added formaldehyde (27 mL, 35–37%) and the mixture was stirred at reflux for 7 h. The solvent was removed under reduced pressure and the crude material was chromatographed on silica gel eluting with EtOAc/MeOH (9.5:0.5, v/v) to afford **2** as a white powder (yield: 5.47 g, 91%).  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.34 (br s, 1H, OH), 5.66 (s, 2H,  $\text{CH}_2$ , linker), 7.60–7.78 (m, 3H, Ar), 8.12 (s, 1H, Ar), 8.35 (m, 1H, Ar). Anal. Calcd for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_2$  (176.17): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.31; H, 4.54; N, 15.86.
- Synthesis of 1-(oxophthalazin-1(2*H*)-yl)methyl 2,2,2-trichloroacetimidate (**3**). To a solution of 2-(hydroxymethyl)phthalazin-1(2*H*)-one (**2**) (0.88 g, 5 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (35 mL) were added sequentially trichloroacetonitrile (5 mL, 50 mmol) and DBU (100  $\mu\text{L}$ ). The reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The resulting residue was purified using silica gel pad filtration, eluting with 5%  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$  and the eluent was evaporated to dryness to give trichloroacetimidate **3** as a pale-yellow oil (yield: 1.43 g, 89%).  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.29 (s, 2H,  $\text{CH}_2$ ), 7.64–7.83 (m, 3H, Ar), 8.15 (s, 1H, Ar), 8.39 (d,  $J$  = 7.4 Hz, 1H, Ar), 8.56 (s, 1H, NH).  $^{13}\text{C}$  NMR (66.2, MHz,  $\text{CDCl}_3$ ):  $\delta$  = 93.4, 126.2, 127.0, 127.5, 129.6, 131.9, 133.8, 138.9, 159.5, 161.4. Anal. Calcd for  $\text{C}_{11}\text{H}_8\text{Cl}_3\text{N}_3\text{O}_2$  (320.56): C, 41.21; H, 2.52; Cl, 33.18; N, 13.11. Found: C, 41.15; H, 2.55; Cl, 33.24; N, 13.15.
- General synthetic procedure for the reaction between trichloroacetimidate and C- and O-nucleophiles. A solution of **3** (0.48 g 1.5 mmol) and the appropriate nucleophile (1.5 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (25 mL) was cooled to  $-78^\circ\text{C}$  and stirred until complete dissolution of the reactants. The solution was treated with TMSOTf (33 mL, 0.15 mmol) and the reaction mixture was further stirred for 20–120 min at the same temperature. The reaction was then quenched by adding sodium bicarbonate (solid) and the reaction mixture was filtered and finally concentrated. The crude material was chromatographed on silica gel, with gradient elution with hexanes/EtOAc.
- 2-(2,4-Dimethoxybenzyl)phthalazin-1(2*H*)-one (**15**). Yellow solid; mp 93–94  $^\circ\text{C}$ ; yield: 0.39 g, 89%.  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.74 (s, 3H,  $\text{OCH}_3$ ), 3.80 (s, 3H,  $\text{OCH}_3$ ), 5.39 (s, 2H,  $\text{CH}_2$ , linker), 6.43 (dd,  $J_1$  = 2.3 Hz,  $J_2$  = 8.3 Hz, 1H, Ar), 6.45 (d,  $J$  = 2.3 Hz, 1H, Ar), 7.09 (d,  $J$  = 8.3 Hz, 1H, Ar), 7.69–7.76 (m, 3H, Ar), 8.14 (s, 1H, Ar), 8.42 (d,  $J$  = 7.1 Hz, 1H, Ar);  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  48.9 ( $\text{CH}_2$ , linker), 55.2 ( $\text{OCH}_3$ ), 55.4 ( $\text{OCH}_3$ ), 98.5 (Ar), 104.1 (Ar), 117.6 (Ar), 125.8 (Ar), 126.7 (Ar), 127.9 (Ar), 129.5 (Ar), 129.7 (Ar), 131.3 (Ar), 132.8 (Ar), 137.6 (Ar), 158.3 (C=O), 159.4 (C=O), 160.2 (C=O). Anal. Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$  (296.32): C, 68.91; H, 5.44; N, 9.45. Found: C, 68.89; H, 5.46; N, 9.47.
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- Ali, I. A. I.; El Ashry, E. S. H.; Schmidt, R. R. *Tetrahedron* **2004**, *60*, 4773–4780.
- 2-[(3,5-Dimethoxybenzyloxy)methyl]phthalazin-1(2*H*)-one (**27**). Yellow oil; yield: 0.44 g, 90%.  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.75 (s, 6H, ( $\text{OCH}_3$ )<sub>2</sub>), 4.70 (s, 2H,  $\text{CH}_2$ , linker), 5.67 (s, 2H,  $\text{CH}_2$ , linker), 6.31 (m, 1H, Ar), 6.53 (d,  $J$  = 2.3 Hz, 2H,

Ar), 7.65–7.83 (m, 3H, Ar), 8.16 (s, 1H, Ar), 8.45 (d,  $J = 7.0$  Hz, 1H, Ar);  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  55.1 (2OCH<sub>3</sub>), 71.6 (CH<sub>2</sub>, linker), 79.1 (CH<sub>2</sub>, linker), 99.8 (Ar), 105.1 (2C, Ar), 126.0 (Ar), 126.9 (Ar), 127.8 (Ar), 129.7 (Ar), 131.7 (Ar), 133.4 (Ar), 138.1 (Ar), 140.0 (Ar), 160.0 (C=O), 160.6 (2COCH<sub>3</sub>). Anal. Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> (326.35): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.22; H, 5.57; N, 8.57.

32. Methyl 4-[[[(1-oxophthalazin-2(1H)-yl)methoxy]methyl]benzoate (**28**). Colorless thick oil; yield: 0.43 g, 88%.  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.88 (s, 3H, OCH<sub>3</sub>),

4.80 (s, 2H, CH<sub>2</sub>, linker), 5.68 (s, 2H, CH<sub>2</sub>, linker), 7.43 (d,  $J = 8.1$  Hz, 2H, Ar), 7.67–7.86 (m, 3H, Ar), 7.95 (d,  $J = 8.1$  Hz, 2H, Ar), 8.17 (s, 1H, Ar), 8.43 (d,  $J = 7.1$  Hz, 1H, Ar).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  51.8 (OCH<sub>3</sub>), 71.0 (CH<sub>2</sub>, linker), 79.2 (CH<sub>2</sub>, linker), 126.1 (Ar), 126.9 (Ar), 127.0 (2C, Ar), 127.7 (Ar), 129.2 (Ar), 129.4 (2C, Ar), 129.6 (Ar), 131.8 (Ar), 133.3 (Ar), 138.3 (Ar), 142.9 (Ar), 160.0 (C=O), 166.7 (C=O). Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (324.33): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.69; H, 4.96; N, 8.65.