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A FACILE AND CONVENIENT SYNTHESIS OF 1*H*-ISOINDOLE-1,3(2*H*)-DIONES

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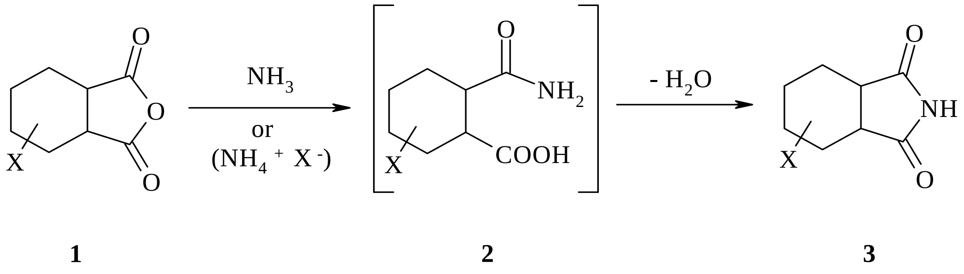
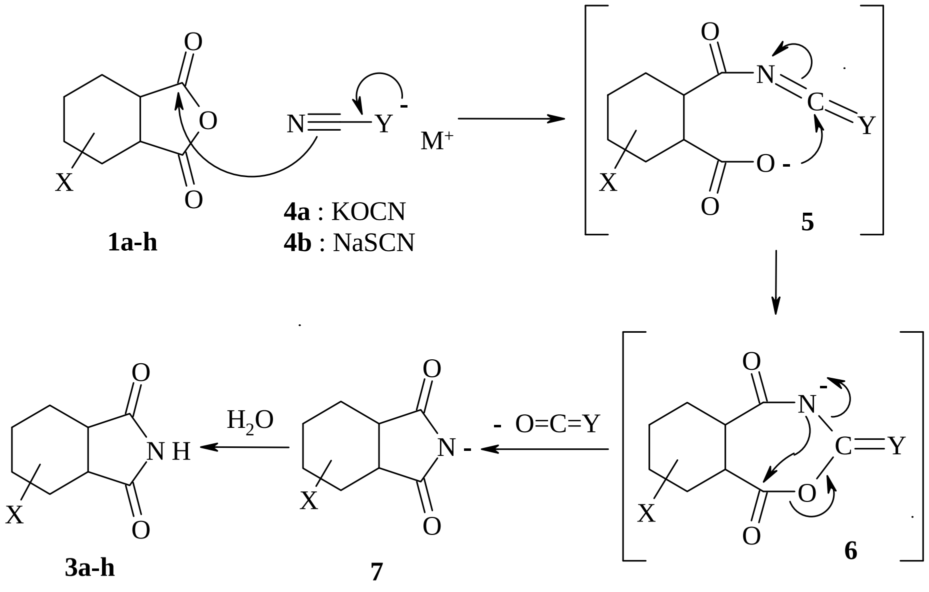
Abstract – A facile synthesis of 1*H*-isoindole-1,3(2*H*)-diones (**3a-h**) has been developed by the reaction of the corresponding anhydrides (**1a-h**) with potassium cyanate (**4a**) or sodium thiocyanate (**4b**). The reactions were carried out in neutral media under reflux or under microwave irradiation without use of catalyst. Good to excellent yields of the products were obtained in high purity with very simple work-up.

Cyclic imides are extensively used in organic synthesis.[1] Since many compounds containing this heterocyclic nucleus are of biological or pharmacological interest,[2-4] methods for the preparation of cyclic imides skeletons, particularly 5-membered imides, have been extensively studied.[5] Owing to their acidity and the reactivity of secondary imides, the nitrogen atom of cyclic secondary imides may be easily functionalized which makes cyclic tertiary imides versatile building blocks.[6] In general, cyclic secondary imides, most commonly 1*H*-isoindole-1,3(2*H*)-diones (phthalimides), are formed by the reaction of the corresponding anhydrides (**1**) with ammonia or its salts. The reaction proceeds through phthalamic acid intermediates (**2**), which in the second step cyclize to form the phthalimides (**3**) (Scheme 1).



Scheme 1

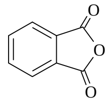
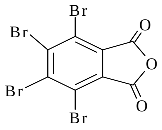
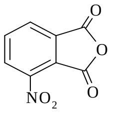
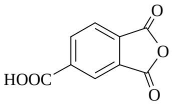
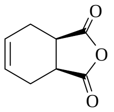
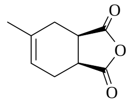
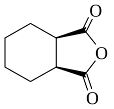
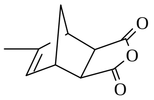
Here, we describe a practical and simple procedure for the synthesis of secondary phthalimide derivatives (**3**) by reaction of phthalic anhydride derivatives (**1**) with potassium cyanate (**4a**) or sodium thiocyanate[7] (**4b**). This method could also be utilized for the synthesis of a variety of cyclic secondary imides other than five-membered imides. There is, so far, no report to use of metallic salts of cyanate or thiocyanate in the synthesis of phthalimide derivatives. A plausible mechanism is shown in Scheme 2.



Scheme 2

We have found that when a mixture of phthalic anhydride derivatives (**1a-h**) and potassium cyanate (**4a**) or sodium thiocyanate (**4b**) was refluxed in dimethylformamide (DMF), the corresponding imides (**3a-h**) were generated in good yields. Extending of our previous works,[5a, 8, 9] employing microwave-assisted conditions, we carried out these reactions under microwave irradiations[10] in DMF, which was recognized as an excellent energy-transfer medium, to reduce the reaction time. As expected, the reaction proceeded fastly to give the imides (**3a-h**) in good to excellent yields within 10 min. However, even under microwave irradiation, the reaction did not proceed under solvent free or solid state conditions. The reaction also proceeded in a green solvent, aqueous ethanol, in place of DMF in the presence of KOCN (**4a**) under microwave irradiation. These facts indicated that microwave irradiations cause faster energy transfer to chemical bonds relative to the classical heating (refluxing) to accelerate molecular rotation and, thus, reaction rate leading to a significant time saving and often improving product yields. In all cases, the products (**3a-h**) were isolated in neutral media with easy work-up. As it is observed, the cyanate (**4a**) gives better yield than the thiocyanate (**4b**) probably because of stronger nucleophility of its nitrogen atom in the former reagent[7] (Table 1).

Table 1 : Synthesis of compounds (**3a-h**)^a from the reaction of **1a-h** with KOCN (**4a**) or NaSCN (**4b**)

		Reflux in DMF				Microwave irradiation in DMF (or EtOH/H_2O)					
		KOCN (**4a**)		NaSCN (**4b**)		KOCN (**4a**)			NaSCN (**4b**)		
1		Time (hour)	Yield **3** (%)^b	Time (hour)	Yield **3** (%)^b	Power (watt)	Time (min.)	Yield **3** (%)^b	Power (watt)	Time (min.)	Yield **3** (%)^b
a		3	88	5	80	500 (500)^c	0.6 (2)^c	92 (90)^c	500	2	80
b		6	83	8	78	600 (600)^c	3 (5)^c	89 (80)^c	600	5	75
c		7	78	8	71	500 (500)^c	2 (6)^c	80 (68)^c	500	3	72
d		7	80	8	74	700 (600)^c	2 (5)^c	77 (73)^c	600	3.5	67
e		5	85	6	79	600 (600)^c	0.5 (5)^c	75 (70)^c	600	5	62
f		5	88	6	80	400 (500)^c	2 (2)^c	80 (65)^c	400	5	75
g		5	78	6	77	500 (600)^c	3 (4)^c	78 (75)^c	500	5	65
h		6	84	7	79	600 (700)^c	8 (6)^c	83 (74)^c	600	8	60

^{a} All products were identified and characterized by physical and spectral data. ^{b} Isolated yields. ^{c} In EtOH/H_2O.

In conclusion, the synthesis of some cyclic secondary imides is developed by the reaction of corresponding anhydrides with potassium cyanate or sodium thiocyanate in neutral media. This is a facile and clean method for the synthesis of cyclic secondary imides, particularly phthalimide derivatives. The reactions proceed without use of catalyst to produce good to excellent yields of the products in high purity with very simple work-up.

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7. Cyanates or thiocyanates are ambident nucleophiles. When the counter ions are Na^+ and K^+, **A** and **C** are predominant and N-terminal has higher nucleophilicity than O-terminal and S-terminal. However, when the counter ion is NH_4^+, the nucleophilicity is inversed. For example, see: (a) M. Moghadam, S. Tangestaninejad, V. Mirkhani, and R. Shaibani, *Tetrahedron*, 2004, **60**, 6105. (b) H. Sharghi, M. A. Nasseri, and A. Hassani-Najad, *J. Mol. Cat. A: Chem.*, 2003, **206**, 53. (c) D. Beaupère, A. E. Meslouti, P. Lelièvre, and R. Uzan, *Tetrahedron Lett.*, 1995, **36**, 5347.

$$\underset{\mathbf{A}}{{}^{-}O{-}C{\equiv}N} \rightleftharpoons \underset{\mathbf{B}}{O{=}C{=}N^{-}} \quad ; \quad \underset{\mathbf{C}}{{}^{-}S{-}C{\equiv}N} \rightleftharpoons \underset{\mathbf{D}}{S{=}C{=}N^{-}}$$

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9. F. Nikpour and T. Paybast, *Chem. Lett.*, 2005, **34**, 1438.
10. There is a considerable interest in the rapid synthesis of a variety of heterocyclic compounds under microwave irradiation, see: (a) C. O. Kappe, *Angew. Chem. Int. Ed.*, 2004, **43**, 6250. (b) Y. Xu and Q.-X. Guo, *Heterocycles*, 2004, **63**, 903. (c) A. de la Hoz, A. Diaz-Ortiz, and A. Moreno, *Chem. Soc. Rev.*, 2004, **34**, 164. (d) N. E. Leadbeater, *Chem. Commun.*, 2005, 2881. (e) V. Molteni and D. A. Ellis, *Curr. Org. Synth.* 2005, **2**, 333. (f) B. A. Roberts and C. R. Strauss, *Acc. Chem. Res.*, 2005, **38**, 653.

Microwave irradiations were carried out in a Butane oven Model MB310. The starting materials

were purchased (Merck) and used.

Caution! For more safety, especially when DMF are used in microwave oven, all experiments should be performed in an efficient hood in order to avoid the contact of vapors.

General procedure:

A mixture of 1 mmol carboxylic anhydrides (**1a-h**), 0.08 g (1 mmol) of KOCN and 0.5 mL of DMF or 1 mL of EtOH/H_2O contained in a 15 mL beaker (equipped with a simple funnel) was placed in the microwave oven and irradiated as indicated in Table 1. After completion of the reaction, the precipitate was cooled to room temperature, then, 3 mL of ice-water was added and mixed with the contents and filtered (three times). In reflux conditions, after completion of the reaction, the solvent was removed under reduced pressure and then, the mixture was washed with ice-water (three times). The products were collected and dried first in air and then in oven (50 ^oC). The raw products were recrystallized from EtOH, n-hexane/ EtOH or EtOH /AcOH.

Compound 2a: mp 236-238 ^oC [238 ^oC[11]].

Compound 2b: mp >330 ^oC [>370 ^oC[12]].

Compound 2c: mp 215-216 ^oC [214-215 ^oC[13]].

Compound 2e: mp 135-137 ^oC [136-137 ^oC[14]].

Compound 2d: White crystals from EtOH, mp 223-230 ^oC.
IR (KBr): ν = 3215-2540, 1781, 1709, 1684 cm^{-1}.

^1H NMR (200.1 MHz) in DMSO-d_6: δ (ppm) = 7.87 (d, $^3J_{HH}$ = 7.7 Hz, 1H, arom. H), 8.18 (s, 1H, arom. H), 8.31 (d, $^3J_{HH}$ = 7.7 Hz, 1H, arom. H), 11.48 (s, 1H, NH), 12.23 (bs, 1H, COOH)

^{13}C NMR (50.3 MHz) in DMSO-d_6: δ (ppm) = 173.23, 170.71, 167.34, 141.16, 140.78, 139.98, 137.91, 128.09, 128.03.

EI-MS (70 eV): *m/z* (%) = 191 ($M^{+\cdot}$, 90), 174 (M^+ - OH, 100), 146 (M^+ - CO_2H, 58), 104 ($C7H4O^+$, 67), 76 ($C6H4^+$, 78).

Compound 2f: White crystals from n-hexane/ EtOH, mp 96-98 ^oC.
IR (KBr): ν = 3215, 1764, 1711 cm^{-1}.

^1H NMR (200.1 MHz) in $CDCl_3$: δ (ppm) = 1.72 (s, 3H, CH_3), 2.38-2.14 (m, 2H, CH_2), 2.56-2.40 (m, 2H, CH_2), 3.16-3.01 (m, 2H, 2CH), 5.54 (dd, $^3J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 1.6 Hz, 1H, =CH), 8.82 (bs, 1H, NH).

^{13}C NMR (50.3 MHz) in $CDCl_3$: δ (ppm) = 181.45, 177.2, 136.09, 119.81, 40.49, 40.00, 28.13, 23.67, 23.21.

EI-MS (70 eV): *m/z* (%) = 165 ($M^{+\cdot}$, 94), 94 (M^+ - CO - HNCO, 70), 93 ($C_7H_9^+$, 88), 91 ($C_7H_7^+$, 38), 79 ($C_6H_7^+$, 100), 77 ($C_6H_5^+$, 3).

Compound 2g: White crystals from n-hexane/EtOH, mp 120-123 ^oC.
IR (KBr): ν = 3210, 1774, 1751, 1718 cm^{-1}.

^1H NMR (200.1 MHz) in $CDCl_3$: δ (ppm) = 1.49-1.43 (m, 4H, $2CH_2$), 1.84-1.79 (m, 4H, $2CH_2$), 2.96-2.84 (m, 2H, 2CH), 8.37 (bs, 1H, NH).

^{13}C NMR (50.3 MHz) in $CDCl_3$: δ (ppm) = 179.74, 40.75, 23.45, 21.51.

EI-MS (70 eV): *m/z* (%) = 153 ($M^{+\cdot}$, 39), 82 (M^+ - CO - HNCO, 97), 67 ($C_5H_7^+$, 100), 54 ($C_4H_6^{+\cdot}$, 51).

Compound 2h: White crystals from n-hexane/EtOH, mp 135-138 °C.
IR (KBr): ν = 3216, 1779, 1704, 1693 cm^{-1}.

^{1}H NMR (200.1 MHz) in $CDCl_3$: δ (ppm) = 1.48-1.39 (m, 2H, CH_2), 1.79 (s, 3H, CH_3), 2.78-2.68 (m, 2H, 2CH), 3.00 (s, 1H, CH), 3.19 (s, 1H, CH), 5.77 (s, 1H, =CH), 8.70 (bs, 1H, NH).

^{13}C NMR (50.3 MHz) in $CDCl_3$: δ (ppm) = 178.51, 178.34, 147.72, 129.95, 50.71, 49.31, 48.23, 44.84, 42.15, 14.90.

EI-MS (70 eV): *m/z* (%) = 177 ($M^{+\cdot}$, 9), 91 ($C_7H_7^+$, 11), 80 ($C_6H_8^{+\cdot}$, 100), 79 ($C_6H_7^+$, 35), 77 ($C_6H_5^+$, 3).

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