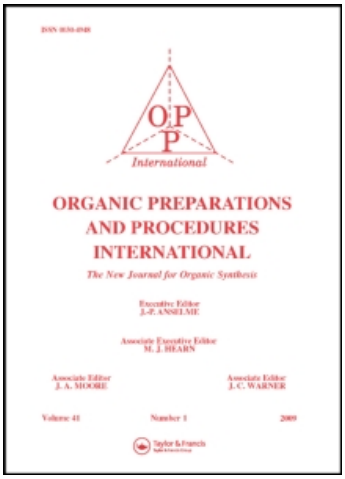

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SIMPLE AND RAPID SYNTHESIS OF BIOLOGICALLY ACTIVE PHTHALIMIDE AND *N*-HYDROXYPHTHALIMIDE DIMERS USING POLYMER-SUPPORTED ANIONS †,††

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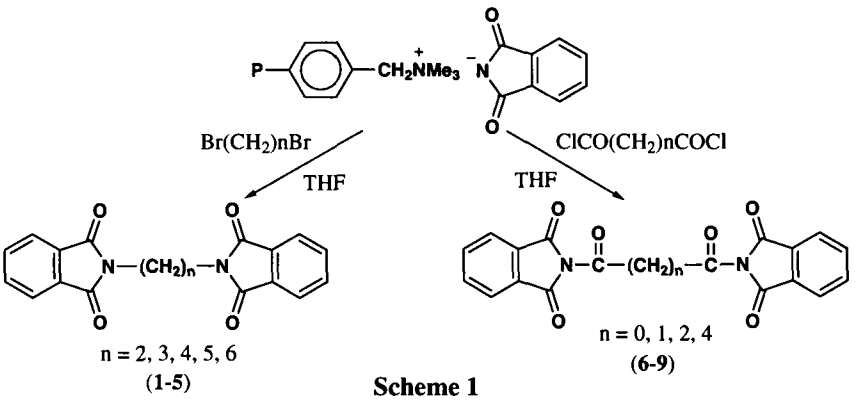
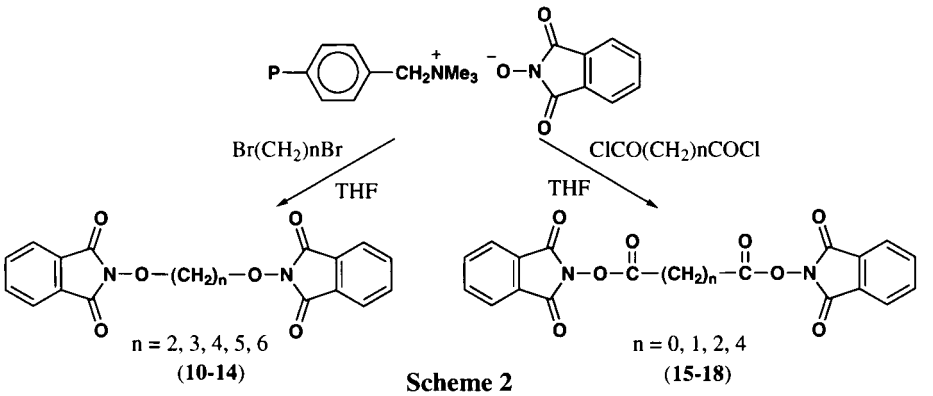
Compounds containing a phthalimide moiety are distinguished by their potent fungicidal action.[1,2] Phthalimide and *N*-hydroxyphthalimide are important intermediates for the preparation of primary amines, *O*-substituted hydroxylamines, agricultural pesticides and are also used in preservatives, pigments and pharmaceuticals.[1-3] The phthaloyl group is a well-established protective group for primary amines[4] in various types of compounds, particularly peptides,[5] aminoglycosides[6] and β-lactam antibiotics.[7] Derivatives of both phthalimide and *N*-hydroxyphthalimide have been reported to possess good antibacterial efficacy and antifungal potency.[8,9] However, a literature survey has revealed that the synthesis of phthalimide[10-14] and *N*-hydroxyphthalimide[15-17] dimers requires strictly anhydrous conditions with high temperature and long reaction times. Furthermore, purification of compounds is compulsory and tedious. In continuation of our work on polymer-supported reactions,[8,9,18,19] we report herein a simple, rapid and environmentally friendly method for synthesis of phthalimide and *N*-hydroxyphthalimide dimers in better yields with higher purity under mild conditions.

Amberlite IRA-400 (chloride form) resin was used to support the phthalimide and *N*-hydroxyphthalimide anions. The α,ω-dibromoalkanes and diacid chlorides were added to the phthalimide and *N*-hydroxyphthalimide anion-supported resin in THF and the mixture was stirred until the reaction was complete, as monitored by silica gel TLC [*Schemes 1 and 2*]. The



Scheme 1

present work appears to be an attractive alternative due to its experimental simplicity, high yields and facile isolation of pure products by simple filtration and evaporation of solvent.



Scheme 2

EXPERIMENTAL SECTION

Phthalimide, *N*-hydroxyphthalimide, α,ω-dibromoalkanes and oxalyl chloride were synthetic grade chemicals (s. d. Fine Chem. Ltd., India). THF was freshly distilled prior to use. Malonyl chloride, succinoyl chloride and adipoyl chloride were prepared in the laboratory.[20] Commercial Amberlite IRA-400 (chloride form) resin was activated by treatment with 5 N HCl solution (100 mL) before use. The reactions of phthalimide and *N*-hydroxyphthalimide were monitored by silica gel TLC (pet. ether:$CHCl_3$, 1:1 and pet. ether:methanol, 9:1, respectively). The synthesized products were characterized by their physical constants, ^1H NMR spectroscopy and elemental analysis. Melting points and boiling points are uncorrected.

General Procedure for Supporting Phthalimide and *N*-Hydroxyphthalimide Anions on Amberlite IRA-400.- Phthalimide (100 mmoles) was dissolved in 100 mL of 1N aqueous potassium hydroxide (100 mmoles). The activated Amberlite IRA-400 (chloride form) (60 g) was packed into a column (2 cm diameter and 45 cm length) and the above solution of the potassium salt of phthalimide was eluted slowly (1.5 mL/min). The resin was washed with distilled water, chloride ions and excess of phthalimide anion were removed. It was then washed with ethanol followed by acetone and dried *in vacuo* (10 mm Hg) at 50°C over P_2O_5 for 3 hr.

N-hydroxyphthalimide (100 mmoles) was similarly supported on the resin using 1N aqueous sodium hydroxide (100 mmoles). The exchange capacity of phthalimide and *N*-hydroxyphthalimide anion supported resin was determined by passing aqueous 1 N KCl and 1 N NaCl (100 mL), respectively, through the supported resin (1 g) packed in a column (0.5 cm diameter and 10 cm length). The anion in the eluent was titrated with 0.01 N HCl using methyl orange as an indicator. The exchange capacity of the supported resin was found to be 1.5 mmoles of phthalimide and 1 mmole of *N*-hydroxyphthalimide anion per gram of dry resin.

General Procedure for the Synthesis of α,ω-Diphthalimido (1-5) and α,ω-Diphthalimidooxy Alkanes (10-14).- A mixture of Amberlite IRA-400 phthalimide or *N*-hydroxyphthal-

imide anion supported resin (15 mmoles), α,ω-dibromoalkane (7.5 mmoles) in THF (40 mL) was stirred and refluxed for 45 to 90 min depending on the reactivity of dibromoalkane. The progress of the reaction was monitored by TLC. After completion of the reaction, the resin was filtered and washed with THF (3 x 5 mL). The filtrate was dried over anhydrous sodium sulfate and removal of solvent gave products (**1-5** and **10-14**) in pure form as listed in *Table 1*.

Synthesis of *N*-Acyl (6-9) and *N*-Acyloxy (15-18) Phthalimide Dimers.- The diacid chloride (7.5 mmoles) was added dropwise to a stirred suspension of Amberlite IRA-400 phthalimide or *N*-hydroxyphthalimide anion supported resin (15 mmoles) in THF (40 mL) at room temperature for 10 to 30 min depending on the reactivity of diacid chloride(s). The progress of the reaction was monitored by TLC. After completion of the reaction, the work-up as described above afforded the products (**6-9** and **15-18**) as listed in *Table 1*.

The compounds were characterized by comparison of their physical constants with literature data.[21, 22] Newly synthesized compounds were characterized by ^{1}H NMR and IR spectroscopic methods and elemental analysis.

Table 1. Phthalimide and *N*-Hydroxyphthalimide Dimers

Cmpd No.	n	Yield (%)	mp (°C)	*lit.* [21, 22] (°C)	^{1}H NMR [a] (δ)
1	2	93	232	232-234	----
2	3	92	189	189	----
3	4	92	226	226-227	----
4	5	91	188	188	----
5	6	90	178	178-179	----
6	0	94	257 (dec.)	----	7.05-7.96 (m, 8H, Ar-H)
7	1	92	132	----	3.91 (s, 2H, CH_2); 7.44-7.83 (m, 8H, Ar-H) [b]
8	2	91	99-101	----	2.53 (s, 4H, CH_2CH_2); 7.35-8.13 (m, 8H, Ar-H)
9	4	93	118-119	----	1.63 (m, 4H, middle CH_2); 2.28 (t, 4H, 2 $COCH_2$); 7.54-7.82 (m, 8H, Ar-H) [b]
10	2	96	254	254	----
11	3	95	180	179-181	----
12	4	92	262	260-265	2.06 (m, 4H, middle CH_2CH_2); 3.42 (t, 4H, 2 OCH_2); 7.29-7.87 (m, 8H, Ar-H)
13	5	91	172	172-174	----
14	6	92	175	175-176	----
15	0	96	233 (dec.)	----	7.48-8.09 (m, 8H, Ar-H) [b]
16	1	93	165	165-167	----
17	2	94	141	140-141	----
18	4	95	172-175 (dec.)	----	1.67 (m, 4H, middle CH_2CH_2); 2.26 (t, 4H, 2 $COCH_2$); 7.46-7.85 (m, 8H, Ar-H) [b]

a) $CDCl_3$ b) $CDCl_3$ + DMSO-d_6

Table 2. Elemental Analysis Data for Compounds **1-18**

Cmpd No.	Elemental Analysis Data (Found) C	H	N
1	67.50 (67.24)	3.78 (3.68)	8.75 (8.90)
2	68.26 (68.14)	4.22 (4.34)	8.38 (8.46)
3	68.96 (69.14)	4.63 (4.42)	8.04 (8.27)
4	69.60 (69.72)	5.01 (4.88)	7.73 (7.66)
5	70.20 (70.36)	5.36 (5.22)	7.44 (7.62)
6	62.07 (62.32)	2.32 (2.40)	8.04 (8.22)
7	62.99 (62.86)	2.78 (2.87)	7.73 (7.84)
8	63.83 (63.95)	3.21 (3.34)	7.44 (7.30)
9	65.35 (65.21)	3.99 (4.22)	6.93 (7.12)
10	61.36 (61.57)	3.43 (3.56)	7.96 (8.18)
11	62.29 (62.43)	3.85 (4.15)	7.65 (7.78)
12	63.16 (63.34)	4.22 (4.02)	7.36 (7.54)
13	63.95 (63.79)	4.60 (4.73)	7.10 (7.29)
14	64.69 (64.63)	4.93 (5.07)	6.86 (6.92)
15	56.85 (56.72)	2.12 (1.93)	7.37 (7.52)
16	57.88 (57.80)	2.56 (2.82)	7.10 (7.18)
17	58.83 (59.10)	2.96 (3.09)	6.86 (6.79)
18	60.55 (60.72)	3.69 (3.82)	6.42 (6.55)

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