N-Alkylation of Imides Using Phase Transfer Catalysts under Solvent-free Conditions

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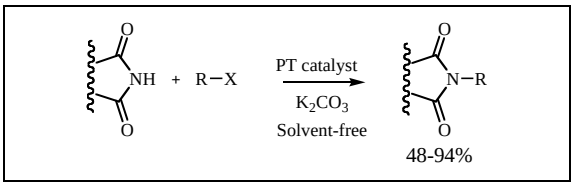
Received January 16, 2008



N-Alkylation of imides in the reaction of imides and alkylhalides, catalyzed by PT catalysts under solvent-free conditions, has been developed. The reaction occurs in the presence of K_2CO_3, and in many cases it takes place spontaneously. In the *N*-benzylation reaction, it has been recognized that TBAB (tetrabutylammonium bromide) and TBATFB (tetrabutylammonium tetrafluoroborate) show highest catalytic effect. Versatility and synthetic capacity of the solvent-free alkylation has been confirmed by *N*-benzylation and *N*-ethylation of various imides. The developed procedure gives easy access to *N*-(ω-bromoalkyl)imides.

J. Heterocyclic Chem., **45**, 1371 (2008).

INTRODUCTION

Imides are important organic compounds, which have been widely used in biology [1]. They are also useful as intermediates in organic synthesis [2] and polymer chemistry [3]. *N*-Alkyl derivatives of imides find broad use in pharmacology. Some *N*-alkyl phthalimides have been applied as antipsychotic [4] and anti-inflammatory [5] agents. Arylpiperazinylalkyl derivatives of phthalimide [6-8], succinimide [6], saccharin [8] and 1,3-benzoxazine-2,4-dione [9] are important compounds used in treatment of various CNS disorders [10]. Hypolipidemic activity [11] and potent specific ability of these compounds to inhibit HIV-1 reverse transcriptase [12] have also been reported.

Synthesis of *N*-alkyl imides was usually accomplished by the reaction of imides with alkyl halides in the presence of a base, such as sodium hydride [13,14], triethylamine [15], KF/Al_2O_3 [6], an organometallic compound (*e.g.*, butyllithium) [16], K_2CO_3 [17-22], Na_2CO_3 [23,24], Cs_2CO_3 [25,26], potassium hydroxide [27] or sodium amide [28]. The reactions were carried out in various solvents, such as acetone [17,18,26,29], DMSO [26], DMF [23,26,30], THF [26], CH_3CN [6,22,25,26,31], xylene [22,32], butan-2-one [19], benzene [20,26], ionic liquids [27,33], or in the presence of excess alkylating agent [17,34]. In solvent-free conditions, *N*-alkylation of potassium salt of phthalimide in the presence of TBAB (tetrabutylammonium bromide) occurs, but the reaction requires heating for a long time [35]. *N*-Alkylation of imides under microwave irradiation in the presence of PEG-400 [36] or TBAB [37] as a phase-transfer catalyst and DMF [36] or acetonitrile [37] as a solvent have also been reported. However, these methods have many disadvantages, such as high reaction temperature, harsh reaction conditions, long reaction time, low yields and sometimes the use of toxic solvents or catalysts. This caused the growth of interests in microwave-enhanced *N*-alkylation of imides without solvent [38].

The reactions under solvent-free conditions were developed in the late eighties [39]. The absence of solvent reduces the risk of explosions. Furthermore, solvents are frequently expensive and sometimes difficult to remove from the reaction mediums.

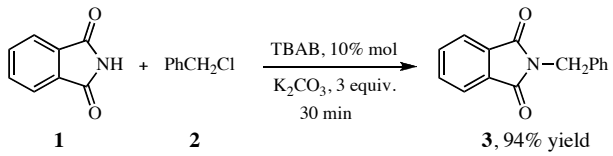
In the present paper, we report an efficient and fast procedure for synthesis of *N*-alkylimides by alkylation of imides under solvent-free conditions, in the presence of K_2CO_3 and a PT catalyst. According to the proposed procedure, the reactions take place spontaneously and afford satisfactory yields.

RESULTS AND DISCUSSION

At the beginning of our study, the reaction of phthalimide (**1**) with benzyl chloride (**2**) in the presence of TBAB as a catalyst was tested, in order to establish the influence of quantity of K_2CO_3 on the reaction yield. Preliminary experiments proved that the progress of the reaction was easy to follow by checking the temperature of the mixture. The mixture left at ambient temperature warmed up spontaneously within 10-15 minutes and after another 15-20 minutes the temperature fell, which signified that the reaction was completed. Obtained results indicate that the highest yield of *N*-benzylphthalimide (**3**) was achieved using 3 equivalents of K_2CO_3, where the mixture heated up to the highest temperature (*i.e.*, 60 °C) in comparison to the other entries

(Scheme 1). Thus, it was recognized that three-fold excess of K_2CO_3 in relation to imide was optimal for that protocol.

Scheme 1



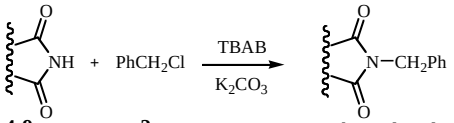
1 **2** **3**, 94% yield

The solid, crude product was separated by filtration after the mixture was poured into water. Thin layer chromatography analysis of **3** (*i.e.*, only one spot corresponding to *N*-benzylphthalimide), correct ir and ^{1}H nmr spectra, as well as mp (*i.e.*, for **3** mp was found as 111-113 °C; 114–116 °C [38], 113–114 °C [36]) indicated that the crude product had good quality. The experiments, where potassium salt of phthalimide was used instead of phthalimide or benzyl chloride was replaced with benzyl bromide to produce **3** with excellent yield (92% and 93%, respectively), indicated that the reaction was not sensitive neither to the form of the phthalimide nor to the type of halogen in the alkylating agent.

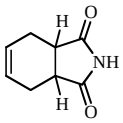
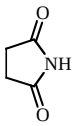
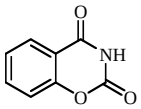
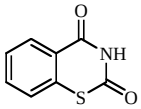
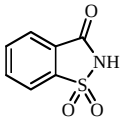
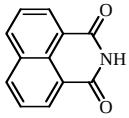
Next, the effect of different PT catalysts on *N*-benzylation of phthalimide was examined. For comparison with TBAB, TBATFB (tetrabutylammonium tetrafluoroborate), TEBA (triethylbenzylammonium chloride), TEAC (tetraethylammonium chloride),

Table 1

N-Benzylation of the imides **4**–**9** under solvent-free conditions [a].



4-9 **2** *N*-benzylimides

Entry	Imide No.	Imide Structure	Reaction time, min	*N*-benzylimide Yield, %	*N*-benzylimide Mp, °C (found)	*N*-benzylimide Mp, °C (reported)
1	**4**		30[b]	94	87–88[c]	Not reported
2	**5**		30[b]	86	101–103	97–99 [Ref. 27] 99.2–100.5 [Ref. 33] 102–103 [Ref. 42]
3	**6**		30[b]	92	133–135	135 [Ref. 43]
4	**7**		30[b]	90	101–103	103 [Ref. 44] 107–108 [Ref. 45]
5	**8**		60[d]	48[e]	110–111	109–110 [Ref. 46]
6	**9**		60[d]	91	192–194	192–194 [Ref. 47]

[a] Reaction conditions: imide (**4**–**9**) (0.010 mol), benzyl chloride (**2**) (0.012 mol), K_2CO_3 (0.030 mol), TBAB (10 mol%). [b] The reaction mixture was left at room temperature. [c] Solvent for crystallization: methanol (colorless needles); ^{1}H nmr (deuteriochloroform): δ 2.05–2.76 (m, 4H, 2xCH_2), 3.10 (dd, 2H, *J* = 7.3, 2.4 Hz, 2xCHCO), 4.63 (s, 2H, CH_2-N-imide), 5.83–5.92 (m, 2H, CH=CH), 7.28 (s, 5H, Ar-H); tlc: R_f = 0.7; ir (potassium bromide): 3043, 2956, 1769, 1697, 1403 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{15}NO_2$ (241.29): C, 74.67; H, 6.27; N, 5.81. Found: C, 74.81; H, 6.34; N, 5.89. [d] The reaction mixture was heated on a boiling water bath. [e] Crystallized from ethyl acetate.

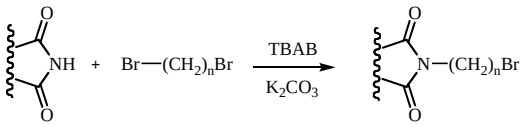
CTMAB (cetyltrimethylammonium bromide), DABCODDI (1,4-di(dodecyl)-1,4-diazabicyclo[2.2.2]-octane diiodide) [40] were selected. The reactions were carried out under previously established optimal conditions. The results indicate that the reaction left at ambient temperature runs efficiently only in the presence of TBAB and TBATFB. In the presence of TEBA, **3** was obtained with 65% yield after 180 min. Similar yield of **3** (62%) was also achieved only after 30 min, but that required heating the mixture on a boiling water bath. Acceleration of the reaction rate after heating was also visible in the use of the remaining PT catalysts (TEAC, CTMAB and DABCODDI). The lack of progress of the reaction in the absence of PT catalysts shows that the presence of a PT catalyst is important for the solvent-free *N*-benzylation of phthalimide.

In order to investigate versatility and synthetic capacity of the solvent-free alkylation of imides, the reaction was further investigated using various imides (Table 1). As shown in Table 1, the *N*-benzylation reaction proceeded efficiently and *N*-benzylimides were obtained in good to excellent yields (48–94%). In the case of *N*-benzylation of saccharine (**8**) and 1,8-naphthalimide (**9**), we did not observe any progress of the reaction at room temperature even after 2 hours. Therefore, the mixture was placed in a boiling water bath that led to the expected product with satisfactory yield after 60 minutes of heating (Table 1, Entry 5 and 6). All obtained crude *N*-benzylimides, except for saccharine (**8**), showed satisfactory purity and additional purification was not necessary.

The procedure developed for solvent-free *N*-benzylation of imides works equally well in the case of *N*-ethylation of the imides **1**, **5** and **6**, however from our point of view, it was interesting to adapt this protocol to the synthesis of *N*-(ω-bromoalkyl)imides. These compounds are the key intermediates for preparation of arylpiperazinylalkyl-imides, investigated by us and by many other researchers as serotonin receptor ligands [9,41]. The reaction of the selected imides **1** and **4**-**8** with 1,ω-dibromoalkanes **10**–**13** were performed under the same conditions as that established for the synthesis of *N*-benzylphthalimide, using 1,ω-dibromoalkane instead of benzyl chloride (Table 2). In order to prevent formation of disubstituted alkylimides, threefold-excess of the dibromoalkane **10**–**13**

Table 2

TBAB-catalyzed synthesis of *N*-(ω-bromoalkyl)imides under solvent-free conditions[a].



1, 4-7 **10-13** *N*-(ω-bromoalkyl)imides

Entry	Imide No.	1,ω-Dibromoalkane No.	Structure	Reaction time, min[b]	*N*-(ω-bromoalkyl)imide Yield, %	Mp, °C (found)	Mp, °C (reported)
1	**1**	**10**	Br—$(CH_2)_2$Br	60	90	80–82	78–80 [Ref. 34]; 80–82 [Ref. 38]
2	**1**	**11**	Br—$(CH_2)_3$Br	60	92	70–71	76 [Ref. 31]
3	**4**	**10**	Br—$(CH_2)_2$Br	30	90	64–66	68–69 [Ref. 48]
4	**4**	**11**	Br—$(CH_2)_3$Br	30	92	52–56	56–58 [Ref. 48]
5	**4**	**12**	Br—$(CH_2)_4$Br	30	88	76–79	78–79 [Ref. 48]
6	**5**	**10**	Br—$(CH_2)_2$Br	60	85	55–56	56–61 [Ref. 19]
7	**5**	**11**	Br—$(CH_2)_3$Br	60	91	49–51	44 [Ref. 20]; 52–53 [Ref. 49]
8	**6**	**10**	Br—$(CH_2)_2$Br	60	91	113–115	111–112 [Ref. 50]
9	**6**	**11**	Br—$(CH_2)_3$Br	60	92	102–103	102–103 [Ref. 51]
10	**6**	**12**	Br—$(CH_2)_4$Br	60	84	64–66	64–66 [Ref. 51]
11	**6**	**13**	Br—$(CH_2)_5$Br	60	85	81–83	81–83 [Ref. 51]
12	**7**	**11**	Br—$(CH_2)_3$Br	60	93	76–77[c]	Not reported

[a] Reaction conditions: imide (**1**, **4**–**7**) (0.010 mol), 1,ω-dibromoalkane (**10**–**13**) (0.030 mol), K_2CO_3 (0.030 mol), TBAB (10 mol%). [b] The reaction mixture was left at room temperature. [c] Solvent for crystallization: methanol (colorless crystals); ^{1}H nmr (deuteriochloroform): δ 2.27 (q, 2H, *J* = 6.7 Hz, $CH_2\underline{CH_2}CH_2$), 3.46 (t, 2H, *J* = 6.8 Hz, Br-CH_2), 4.31 (t, 2H, *J* = 6.8 Hz, CH_2-N-imide), 7.30–7.71 (m, 3H, Ar-H), 8.39 (dd, 1H, *J* = 7.4, 2.2 Hz, Ar-H); tlc: R_f = 0.8. ir (potassium bromide): 3066, 2975, 1682, 1639, 1443, 1341 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{10}BrNO_2S$ (300.17): C, 44.01; H, 3.36; N, 4.67. Found: C, 44.21; H, 3.20; N, 4.75.

was used. In all reactions the mixture left at room temperature heated up spontaneously. Nevertheless, the thermal effect decreased with increase of the carbon chain length in 1,ω-dibromoalkanes. When 1,2-dibromoethane (**10**) was used for alkylation of **6**, the mixture heated up to about 60 °C, however, when 1,5-dibromopentane (**15**) was applied, the maximal temperature reached only 40 °C. While in the case of the imide **4** the reaction was complete after 30 min, the reaction time required for the imides **1**, **5**–**7** was 60 min (Table 2).

In summary, we have developed a fast and easy method for *N*-alkylation of imides under solvent-free conditions using PT catalysts. The reaction mixture stays consistent with that used in the microwave-accelerated *N*-alkylation of phthalimide [38], however, our experiments have demonstrated that this system allows obtaining *N*-alkylimides without external stimulation. In many cases, significant heat evolution was observed during the *N*-alkylations. This may create a potential hazard when the reaction is carried out in larger scale, in particular, when the alkylating agent is volatile.

In the synthesis of *N*-benzyl- and *N*-ethylimides separation of the reaction product is carried out by adding the mixture to water. The product quality is high, and, in many cases, no further purification is required. In the synthesis of *N*-(ω-bromoalkyl)imides, where threefold excess of dibromoalkane is used, the separation of the reaction products is accomplished by extraction. After removal of the solvent and excess of dibromoalkane, crystallization of the crude product is necessary to afford high quality *N*-(ω-bromoalkyl)imides. All of the compounds obtained are known and their structure was confirmed by spectroscopic methods and by comparison of their physical properties with those of the authentic samples (analytical details are omitted at this point).

EXPERIMENTAL

^{1}H nmr spectra were taken on Varian 300 MHz Mercury-VX spectrometer in deuteriochloroform solution using TMS as an internal standard. Melting points were determined on a Böetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer, and the results are within ± 0.4% of the calculated values. Infrared spectra were recorded on a Bio-Rad FTS 175B spectrometer, using pressed potassium bromide discs. The reaction progress and purification quality were monitored by tlc (uv detection) on aluminum sheets coated with silica gel 60 F254 (Merck), using chloroform/methanol (90:10) mixture as eluent. All chemicals were purchased from commercial sources (Sigma-Aldrich and Merck) and were used without further purification.

***N*-Benzylation and *N*-ethylation of imides, general procedure.** A powdered mixture of 0.01 mol of the imide **1** or **4**-**7**, 4.14 g (0.03 mol) of anhydrous potassium carbonate and 0.32 g (0.001 mol) of TBAB were placed in a reaction vessel. Then, 1.2 equivalent of benzyl chloride (**2**) was added and the mixture was stirred with a spatula for *ca*. 1 minute. The mixture was left at ambient temperature. Within 10-15 minutes the mixture warmed up spontaneously to 40-60 °C, and after another 15-20 minutes the temperature dropped down, which signified that the reaction was completed. Separation of the reaction product was carried out by adding the mixture to 100 mL of water and filtration of the suspension formed. The crude *N*-benzylimides obtained in this way had good quality (Table 1). When the same procedure was used for *N*-ethylation of the imides **1**, **5** and **6** with ethyl bromide the yield of *N*-ethylphthalimide (mp 77-78 °C), *N*-ethylsuccinimide (mp 24-26 °C), and *N*-ethyl-1,3-benzoxazine-2,4-dione (mp 109-111 °C) was 90, 86 and 70%, respectively.

***N*-(ω-Bromoalkylation) of imides, general procedure.** The reaction mixture was prepared similarly as that presented for the synthesis of *N*-benzylimides, using 3 equivalents of the appropriate 1,ω-dibromoalkane **10**-**13** instead of benzyl chloride (**2**). The mixture left at ambient temperature warmed up spontaneously, and after 30 to 60 min the reaction was completed (Table 2). Next, the mixture was poured into 100 mL of water, and the products were extracted with chloroform. After evaporation of the solvent and the excess of dibromoalkane, crude products were purified by crystallization.

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