KF/Al_2O_3 as an Efficient Catalyst for the Synthesis of *N*-Alkylphthalimides

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Summary: KF/Al_2O_3 acts as an efficient, green, heterogeneous and reusable catalytic system for the preparation of *N*-alkylphthalimides via Michael addition of phthalimide to α,β-unsaturated esters under solvent-free and mild conditions.

Introduction

In the recent years, evolution of chemical reactions involving less hazardous, environmentally acceptable and recyclable catalytic systems is gaining considerable attention both in industrial and academic research [1-5]. KF/Al_2O_3 is certainly one of these green catalytic systems that has been used in various organic transformations [3-5]. Nevertheless, most of the existing processes in organic synthesis involving toxic and volatile organic solvents as reaction media, which are environmentally unacceptable from green chemistry view point. One of the most useful techniques to solve this problem is solvent-free conditions that makes synthesis simpler, cost effective, saves energy, and prevents solvent waste, hazards and toxicity [6, 7].

N-Alkyl derivatives of phthalimide are significant because of possessing various biological activities such as anti-inflammatory [8], antipsychotic [9], hypolipidemic [10] and receptor properties [11]. Moreover, these compounds are very useful intermediates in organic synthesis as they can be easily converted to primary amines (Gabriel synthesis) [12]. The aza-Michael addition of phthalimide to electrophilic alkenes can be used as a useful synthetic route toward *N*-alkylphthalimides [13-16]. Indeed, to the best of our knowledge, there are only a few reports of Michael reaction of phthalimide in the literature. Moe *et al.* [13] have used Na in absolute EtOH to achieve Michael addition of phthalimide to α,β-unsaturated aldehydes [13]. Cardillo *et al.* [14] have carried out conjugate addition of phthalimide salts to α,β-unsaturated imides in the presence of $AlMe_2Cl$ [14]. Furthermore, more recently we have applied ZnO [15] and 1,4-diazabicyclo[2,2,2]octane [16] for Michael addition of phthalimide to α,β-unsaturated esters. However, these reported methods have one or more of the following disadvantages: (i) moderate yields, (ii) relatively long reaction times, (iii) the use of more reactive phthalimide salts instead of phthalimide, (iv) harsh reaction conditions, (v) difficult experimental procedures, and (vi) the use of stoichiometric catalysts. Therefore, it seems highly desirable to find an efficient, simple, and mild protocol for Michael reaction of phthalimide.

Considering the above facts and also in continuation of our previous studies on green organic synthesis [15-17], we report here an efficient, green and simple synthesis of *N*-alkylated phthalimides *via* Michael addition of phthalimide to α,β-unsaturated esters in the presence of catalytic amount of KF/Al_2O_3 and tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst at 50 °C under solventless conditions (Fig. 1).

Results and Discussion

In order to find the best conditions for the Michael reaction, the effect of temperature, different proportions of KF/Al_2O_3 to substrate and solvent were studied on Michael addition of phthalimide to *n*-butyl acrylate in the presence of TBAB (Fig. 1 and Table-1). As it can be seen from Table-1, the reaction did not efficiently proceed at room temperature;

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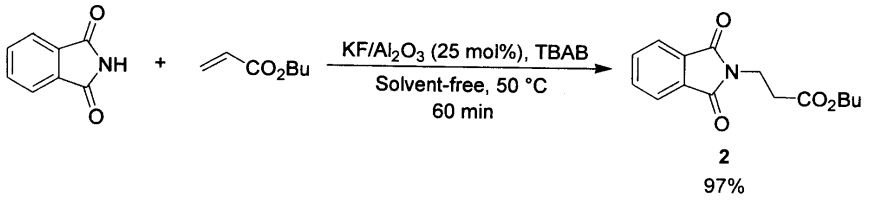


Fig. 1: Michael addition of phthalimide to *n*-butyl acrylate.

Table-1: The effect of temperature, different proportions of KF/Al_2O_3 to substrate and solvent on Michael addition of phthalimide to *n*-butyl acrylate.

T (°C)	*KF/Al_2O_3 (mol%)*	*Solvent*	*Time (min)*	*Yield (%)[a]*
r.t.	25	-[b]	720	19
50	25	-[b]	60	97
70	25	-[b]	50	97
50	15	-[b]	180	75
50	40	-[b]	50	97
50	60	-[b]	40	97
50	25	MeCN	180	76
50	25	EtOAc	180	59
50	25	$CHCl_3$	300	27
50	25	DMF	120	90
50	25	DMSO	80	95

[a]Isolated yield. [b]Solvent-free conditions.

however, enhancing the temperature to 50 °C gave 97 % of the product within 60 min. The best proportion of the catalyst to substrate was found to be 25 mol %. Increasing the amount of the catalyst did not affect significantly on the reaction results. The results also showed that the solvent-free technique is better than solution conditions. Therefore, the conditions: temperature 50 °C, proportion of KF/Al_2O_3 to substrate 25 mol % and solvent-free was selected as the optimized reaction conditions.

Michael addition of phthalimide to *n*-butyl acrylate was also examined in the presence of KF/TBAB as well as Al_2O_3/TBAB separately (Table-2). As Table-2 indicates, these catalysts were not efficient for this transformation. To realize the influence of TBAB on the reaction, the model reaction was checked in the absence of TBAB in which the product was produced in low yield (Table-2). Thus, TBAB has an essential effect on the progress of the reaction. In fact, in this reaction TBAB acts as a phase-transfer catalyst [6, 7]. In another study, the model reaction was tested in the presence of TBAB without KF/Al_2O_3; however, this reaction was not successful even after prolonged reaction time (Table-2).

To recognize the generality and scope of our method, phthalimide was reacted with different α,β-unsaturated esters (Table-3). As Table-3 shows, all reactions proceeded efficiently and the desired Michael adducts were produced in excellent yields relatively short reaction times.

Table-2: Michael addition of phthalimide to *n*-butyl acrylate using KF/TBAB, Al_2O_3/TBAB, KF/Al_2O_3 and TBAB separately at 50 °C.

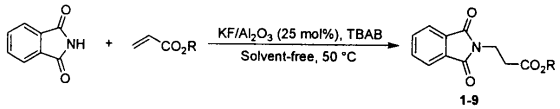
Catalytic System	Time (min)	Yield (%)[a]
KF/TBAB	420	51
Al_2O_3/TBAB	600	8
KF/Al_2O_3[b]	600	16
TBAB[c]	600	-

[a]Isolated yield. [b]This reaction was carried out in the absence of TBAB. [c]This reaction was performed in the presence of TBAB without KF/Al_2O_3.

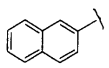
Ease of recycling of the catalytic system is one of the advantage of our method. For the reaction of phthalimide with *n*-butyl acrylate no significant loss of the product yield was observed when KF/Al_2O_3 was used after four times of recycling.

In conclusion, we have developed a new method for the synthesis of *N*-alkyl derivatives of

Table-3: Synthesis of *N*-alkylphthalimides via Michael addition of phthalimide to α,β-unsaturated esters.



1-9

R	Product[a]	Time (min)	Yield (%)[b]
CH_3CH_2	1	60	96
$CH_3(CH_2)_2CH_2$	2	60	97
$CH_3(CH_2)_4CH_2$	3	80	97
$C_6H_5CH_2$	4	80	96
$C_6H_5CH_2CH_2$	5	80	95
$C_6H_5CH{=}CHCH_2$	6	90	96
o-CH_3O-$C_6H_4OCH_2CH(OH)CH_2$	7	150	91
C_6H_5	8	50	95
	9	50	93

[a]All products were identified by comparison of their melting points and ^{1}H-NMR data with those in the authentic samples. [b]Isolated yield.

phthalimide using KF/Al_2O_3 in the absence of solvent. The promising points for the presented methodology are efficiency, high yield, relatively short reaction times, mild conditions, ease of handling and low cost of the catalyst, cleaner reaction profile, ease of product isolation, simplicity, potential of recycling of the catalyst, and finally compliance with the green chemistry protocols.

Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. The ^{1}H NMR (250 MHz) was recorded on a Bruker Avance DPX-250, FT-NMR spectrometer. Melting points were determined on a Büchi B-545 apparatus in open capillary tubes.

General Procedure for the Preparation of KF/Al_2O_3 Catalytic System

A mixture of KF (0.291 g, 5 mmol) and Al_2O_3 (0.510, 5 mmol) was ground vigorously to give KF/Al_2O_3 catalytic system as a white powder (0.801 g).

General Procedure for the Preparation of N-Alkylphthalimides

To a well-ground mixture of phthalimide (0.294 g, 2 mmol), KF/Al_2O_3 (0.080 g, 0.5 mmol) and TBAB (0.322 g, 1 mmol) in a 10 mL round-bottomed flask fitted with connected to a reflux condenser was added α,β-unsaturated ester (2.6 mmol). The resulting reaction mixture was stirred in an oil-bath (50 °C) for the times reported in Table-3. Afterward, the reaction mixture was cooled to room temperature and was suspended in chloroform (50 mL), filtered and the filtrate was washed with water (2×40 mL), and dried with $MgSO_4$. The solvent was evaporated and the crude product was purified by short column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/5).

Ethyl 3-phthalimido propanoate (1)

Colorless solid; M.p. 60-61 °C (Lit. [15] M.p. 60-61 °C). ^{1}H-NMR ($CDCl_3$): δ 1.11 (3H, t, J = 7.1 Hz, CH_3), 2.57 (2H, t, J = 7.2 Hz, O=CCH_2), 3.86 (2H, t, J = 7.2 Hz, NCH_2), 4.06 (2H, q, J = 7.1 Hz, OCH_2), 7.57-7.70 (4H, m, H3-H6 of the aromatic ring).

Butyl 3-phthalimido propanoate (2)

Colorless solid; M.p. 50-51 °C (Lit. [15] M.p. 51-52 °C). ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H, t, J = 6.8 Hz, CH3), 1.28 (2H, m, CH_3CH_2), 1.59 (2H, m, $CH_3CH_2CH_2$), 2.58 (2H, t, J = 7.2 Hz, O=CCH_2), 3.91 (2H, t, J = 7.2 Hz, NCH_2), 4.08 (2H, t, J = 6.9 Hz, OCH_2), 7.64-7.76 (4H, m, H3-H6 of the aromatic ring).

Hexyl 3-phthalimido propanoate (3)

Colorless solid; M.p. 41-42 °C (Lit. [16] M.p. 40-41°C). ^{1}H-NMR ($CDCl_3$): δ 0.89 (3H, t, J = 6.7 Hz, CH_3), 1.29-1.36 (6H, m), 1.60 (2H, m, $CH_3(CH_2)_3CH_2$), 2.59 (2H, t, J = 7.0 Hz, O=CCH_2), 3.95 (2H, t, J = 7.0 Hz, NCH_2), 4.09 (2H, t, J = 6.9 Hz, OCH_2), 7.68-7.83 (4H, m, H3-H6 of the aromatic ring).

Benzyl 3-phthalimido propanoate (4)

Colorless solid; M.p. 58-60 °C (Lit. [16] M.p. 57-59 °C). ^{1}H-NMR ($CDCl_3$): δ 2.59 (2H, t, J = 7.1 Hz, O=CCH_2), 3.86 (2H, t, J = 7.1 Hz, NCH_2), 4.94 (2H, s, OCH_2), 7.08-7.17 (5H, m, H2-H6 of the aromatic ring of alkoxy group), 7.52 (2H, m, H4 and H5 of the aromatic ring of phthalimide), 7.63 (2H, m, H3 and H6 of the aromatic ring of phthalimide).

Phenethyl 3-phthalimido propanoate (5)

Colorless solid; M.p. 53-55 °C (Lit. [15] M.p. 53-55 °C). ^{1}H-NMR ($CDCl_3$): δ 2.69 (2H, t, J = 7.2 Hz, O=CCH_2), 2.87 (2H, t, J = 7.1 Hz, $ArCH_2$), 3.93 (2H, t, J = 7.2 Hz, NCH_2), 4.26 (2H, t, J = 7.1 Hz, OCH_2), 7.13-7.26 (5H, m, H2-H6 of the aromatic ring of alkoxy group), 7.64 (2H, m, H4 and H5 of the aromatic ring of phthalimide), 7.77 (2H, m, H3 and H6 of the aromatic ring of phthalimide).

Cinnamyl 3-phthalimido propanoate (6)

Pale yellow oil; (Lit. [16] oil). ^{1}H-NMR ($CDCl_3$): δ 2.68 (2H, t, J = 7.1 Hz, O=CCH_2), 3.92 (2H, t, J = 7.1 Hz, NCH_2), 4.64 (2H, m, OCH_2), 6.12 (1H, m, ArCH=*CH*), 6.49 (1H, d, J = 15.8 Hz, ArCH), 7.17-7.26 (5H, m, H2-H6 of the aromatic ring of alkoxy group), 7.57 (2H, m, H4 and H5 of the aromatic ring of phthalimide), 7.72 (2H, m, H3 and H6 of the aromatic ring of phthalimide).

2-Hydroxy-3-(2-methoxyphenoxy)propyl 3-phthalimido propanoate (7)

Pale yellow oil; (Lit. [15] oil). ^{1}H-NMR ($CDCl_3$): δ 2.63 (2H, t, J = 7.0 Hz, O=CCH_2), 3.67 (3H, s, CH_3), 3.80-390 (5H, m), 4.11-4.19 (3H, m), 6.73-6.80 (4H, m, H3-H6 of the aromatic ring of alkoxy group), 7.54 (2H, m, H4 and H5 of the aromatic ring of phthalimide), 7.68 (2H, m, H3 and H6 of the aromatic ring of phthalimide).

Phenyl 3-phthalimido propanoate (8)

Colorless solid; M.p. 73-75 °C (Lit. [16] 70-72 °C). ^{1}H-NMR ($CDCl_3$): δ 2.74 (2H, t, J = 7.1 Hz, O=CCH_2), 3.95 (2H, t, J = 7.1 Hz, NCH_2), 6.98 (2H, d, J = 8.0 Hz), 7.09 (1H, d, J = 6.9), 7.24 (2H, dd, J = 6.9, 8.0 Hz), 7.61-7.73 (4H, m, H3-H6 of the aromatic ring of phthalimide).

Naphthalen-2-yl 3-phthalimido propanoate (9)

Pale yellow solid; M.p. 92-94 °C (Lit. [15] M.p. 88-90 °C); ^{1}H-NMR ($CDCl_3$): δ 2.69 (2H, t, J = 7.2 Hz, O=CCH_2), 3.92 (2H, t, J = 7.2 Hz, NCH_2), 7.01-7.08 (3H, m), 7.21-7.31 (3H, m), 7.55-7.64 (3H, m), 7.76 (2H, m, H3 and H6 of the aromatic ring of phthalimide).

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