2-Methyltetrahydrofuran as a suitable green solvent for phthalimide functionalization promoted by supported KF†

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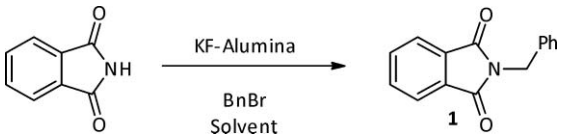
An efficient chemoselective nitrogen functionalization of phthalimides by using KF-Alumina in 2-methyltetrahydrofuran, a solvent obtained from renewal sources, is described.

The isoindoline-1,3-dione nucleus (phthalimide) is present as the pharmacophoric structure in many biologically active compounds, the most representative probably being thalidomide, a drug used in the late 1950s and early 1960s as a sedative and to prevent nausea during pregnancy, whose (*S*)-enantiomer (*distomer*) was shown to cause severe fetal malformations (phocomelia) when taken during first trimester of pregnancy.[1] Nowadays, the interest towards this compound has been rekindled because of the anti-inflammatory and antiangiogenic properties of the (*R*)-enantiomer (*eutomer*), as well as its potential use in the treatment of HIV[2,3] and cancer.[4,5]

Due to such biological, pharmaceutical and industrial importance, the synthesis of isoindole-1,3-diones has received considerable attention in literature.[6,7] The most common method employed for their preparation involves the dehydrative condensation of phthalic anhydride and a primary amine under different conditions (MW irradiation,[8,9] Lewis acids,[10,11] ionic liquids[12] or condensation under high-temperature and high pressure conditions (HTHP)[13]), just to improve the normally low yields recovered in the absence of any specific activation procedure. The last technique mentioned above, because of the extreme experimental conditions required (1240–1650 psi; 263–332 °C), noticeably illustrates the chemoselectivity problems related to the reactivity of water-labile functionalities, as well as the problems caused by the electronic nature of the amine used. On the other hand, this procedure clearly violates the 6th principle of Green Chemistry, which demands energy efficiency by employing synthetic methods conducted at mild temperatures and atmospheric pressure.[14]

Thus, in order to develop more sustainable organic processes by using supported reagents and eco-friendly solvents (*i.e.* 2-methyltetrahydrofuran, MeTHF), we evaluated the possibility to use it as a solvent for the *N*-functionalization of different phthalimide derivatives. In fact, recently MeTHF has been proposed as a good solvent for organometallic reactions (Grignard chemistry, Reformatsky reaction, lithiations, hydride reductions, coupling reactions)[15] and for regioselective biotransformations,[16] showing to be a better choice compared to THF[15] or dichloromethane in biphasic reactions.[17] The fact that its precursor (furfural) is derived from renewable sources (corncobs or bagasse), is in accordance with the 7th principle of Green Chemistry,[14] and its use will render greener processes, as the 3R considerations (reduce, recycle and reuse) are all met by the introduction of MeTHF. On the other side, the use of supported potassium fluoride has proven to be highly beneficial to obtain high chemoselective protocols both in nitrogen functionalization[18] and phthalimide chemistry.[19]

Table 1 *N*-benzylation of phthalimide under different conditions



Entry	Base	Solvent	Reaction time/h	*T*/°C	Yield (%)
1	KF–Al_2O_3	CH_3CN	12	83	86
2	KF–Al_2O_3	CH_3CN	24	60	65
3	KF–Al_2O_3	DMF	12	90	78
4	KF–Al_2O_3	THF	12	66	74
5	KF–Al_2O_3	MeTHF	6	83	98
6	KF–Al_2O_3	MeTHF	12	66	82
7	KF–Al_2O_3	Toluene	24	90	35
8	KF–Al_2O_3	$CHCl_3$	24	77	27
9	KF-Celite	CH_3CN	24	83	17
10	KF-Celite	MeTHF	24	83	31
11	KF–Al_2O_3[a]	MeTHF	24	83	36

[a] Reaction Conditions: base (1.5 equiv.); benzyl bromide (1.0 equiv.); phthalimide (1.2 equiv.). (a) 0.15 equiv. of base were used.

In this communication, we present a convenient procedure for the *N*-functionalization of a series of phthalimide derivatives promoted by supported KF in MeTHF. As Bayer and coworkers reported the preparation of *N*-benzylphthalimide **1**, promoted by CsF-Celite in refluxing acetonitrile (86% yield after 48 h),[20] the use of a more basic reagent such as KF–Al_2O_3[21,22] was tested just to try to reduce the reaction time. The results are shown in Table 1.

As can be seen, the efficiency of this base seemed to be solvent and temperature dependent: reactions performed in polar aprotic solvents (entries 1–6) were faster and more efficient than those carried out in apolar solvents (entries 7 and 8). On the other hand, as temperature was increased, the reaction yields were higher, and reaction time decreased (entries 1, 3–6). Among

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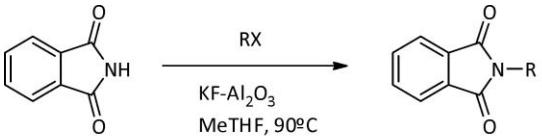
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for all new compounds and HPLC data. See DOI: 10.1039/c0gc00113a

Table 2 *N*-functionalization of phthalimide with primary and secondary electrophiles



2a-e (RX = allylic halides)
3a-c (RX = secondary alkyl halides)

Entry	Electrophilic agent	Reaction time/h	Isolated yield (%)
1	allyl iodide	4	**2a** (95)
2	1-iodo-3-methylbut-2-ene	4	**2b** (93)
3	2-chloro-3-iodoprop-1-ene	5.5	**2c** (84)
4	2,3-dibromoprop-1-ene	6.5	**2d** (88)
5	3-iodo-2-methylprop-1-ene	7	**2e** (87)
6	cyclohexyl chloride	12	**3a** (89)
7	*sec*-butyl bromide	12	**3b** (66)
8	*iso*-propyl bromide	8	**3c** (76)

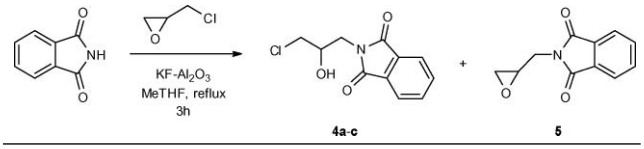
all solvents tested MeTHF proved to be the best, and reflux conditions allowed maximization of the yield and reducing time (entry 5). Base-carrier played a determinant role, as evidenced by the low yields observed with KF-Celite (entries 9–10). Finally, the poor result obtained in the presence of catalytic amounts of KF-Alumina (entry 11), clearly indicated that it was not acting as a catalyst, but rather as a simple heterogeneous base, requiring a slight stoichiometric excess.

Thus, these good preliminary results prompted us to start an exhaustive study concerning the application of the (KF-Alumina/MeTHF) system for phthalimide *N*-functionalization protocols.

Among the series of allylic electrophiles, selected because of their widely functionalization capability,[23] it was possible to recover excellent yields of the corresponding allylated adducts (Table 2, **2a–e**) with only small differences depending on the steric hindrance of the vicinal position to the halogen leaving group, which caused a detectable increase in reaction times (entries 1–5). Secondly, we focused our attention towards the use of secondary alkyl halides, which, in principle, could also lead to the corresponding elimination products, as previously described for alkylations carried out with the potassium phthalimide salt.[24] Nevertheless, cyclohexyl chloride (Table 2, entry 6), under our experimental conditions exclusively led to the nucleophilic displacement product **3a** in high yield (89%), without any trace of the elimination product as previously reported.[24] Similarly, *sec*-butyl bromide (entry 7) and isopropyl bromide (entry 8) only afforded the substitution product. Although the reaction times for secondary halides are in all cases longer compared to the corresponding primary counterparts, the absence of any elimination by-product under our experimental conditions is in clear accordance with the Atom Economy recommended by the 2nd principle of Green Chemistry.[14]

As a next step, we turned our attention to dielectrophilic reagents such as epichlorohydrins, which could lead to two different substitution products, the halohydrin or the epoxide, depending on the regioselective pathway of the reaction, as depicted in the scheme for Table 3.

Table 3 Epoxide ring-opening by phthalimide promoted by KF-Alumina/MeTHF protocol

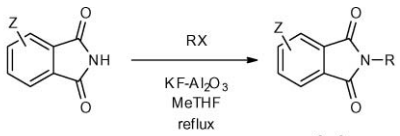


4a-c **5**

Entry	Epoxide	**4** (%)	**5** (%)	Ratio (**4**/**5**)	**4** ee [b] (%)
1	*rac*-epichlorohydrin	**4a** (86)	12	7.2	—
2[a]	*rac*-epichlorohydrin	**4a** (54)	31	1.7	—
3	(*S*)-epichlorohydrin	(*R*)-**4c** (85)	11	7.7	92
4	(*R*)-epichlorohydrin	(*S*)-**4b** (83)	10	8.3	95

[a] Reaction performed at 60 °C during 24 h. [b] Measured by HPLC equipped with a Chiralcel AD chiral column (see ESI).

Table 4 KF-Alumina in MeTHF promoted *N*-functionalization of differently substituted phthalimides



6a-9

Z = 3-nitro; R = methyl (**6a**)
Z = 3-nitro; R = allyl (**6b**)
Z = 3-nitro; R = 1-(2-chloroallyl) (**6c**)
Z = 4-nitro; R = methyl (**7a**)
Z = 4-nitro; R = allyl (**7b**)
Z = 4-nitro; R = 1-(2-chloroallyl) (**7c**)
Z = 3-methyl; R = methyl (**8a**)
Z = 3-methyl; R = allyl (**8b**)
Z = 3-methyl; R = 1-(2-chloroallyl) (**8c**)
Z = *o*-C_4H_4; R = 1-(3-chloro-(2*S*)-hydroxypropyl (**9**)

Entry	Z	RX	Reaction time/h	Product/ Yield (%)
1	3-nitro	methyl iodide	4 h	**6a** (88)
2	3-nitro	allyl iodide	3.5 h	**6b** (93)
3	3-nitro	2-chloro-3-iodopropene	4 h	**6c** (86)
4	4-nitro	methyl iodide	5 h	**7a** (91)
5	4-nitro	allyl iodide	5 h	**7b** (95)
6	4-nitro	2-chloro-3-iodopropene	6 h	**7c** (87)
7	3-methyl	methyl iodide	7 h	**8a** (83)
8	3-methyl	allyl iodide	5 h	**8b** (88)
9	3-methy	2-chloro-3-iodopropene	6 h	**8c** (81)
10	*o*-C_4H_4	(*R*)-epichlorohydrin	3 h	**9** (92)

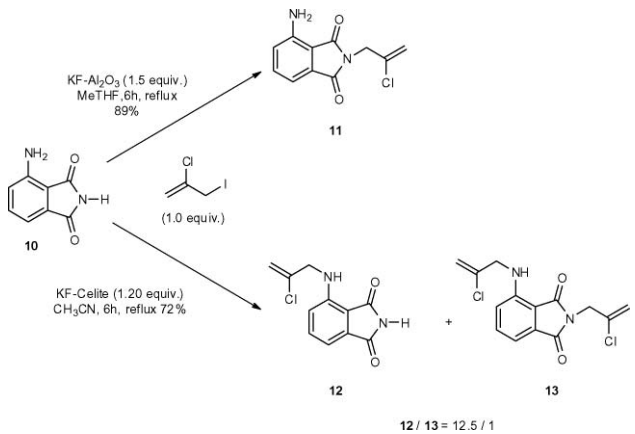
As can be seen from Table 3 temperature is really influential, using the same conditions it is possible to minimize the formation of product **5**, corresponding to chlorine substitution, simply by increasing temperature from 60 °C to reflux (entries 1–2). It is worth highlighting that when both enantiopure forms of epichlorohydrin (entries 3–4) were used, the regioselective ring-opening occurred in parallel with a very good stereospecificity, thus improving previous procedures described[25] for the synthesis of optically active **4b** and **4c**, which are crucial building blocks in the synthesis of β-adrenergic blocking agents.[26]

The efficiency of the proposed *N*-functionalization protocol was afterwards confirmed also in the case of substituted phthalimides (Table 4).

Interestingly, allyl iodide resulted the electrophile leading to the best yields (entries 2, 5 and 8); on the other hand, 2-chloro-3-iodopropene, because of the deactivation of such substituted olefins,[18] afforded lower yields (entries 3, 6 and 9). More acidic 3- and 4-nitrophthalimide reached completion in shorter reaction times (entries 1–6) compared to 3-methylphthalimide

(entries 7–9). Such behaviour was observed also in the case of tricyclic 2,3-naphthalimide (entry 10), which reacted with (*R*)-epichlorohydrin under our optimized conditions, affording uniquely the haloalcohol **9** in excellent regio- and enantioselective fashion.

After confirming that our potassium fluoride supported on alumina-promoted conditions were indeed adequate for promoting *N*-alkylations, we then decided to augment our synthetic efforts towards checking the chemoselectivity of the alkylation reaction, by applying our experimental conditions to 3-aminophtalimide **10**, bearing two potential nucleophilic sites: the NH of the cyclic imide and the arylamino functionality. In fact, the limitation typically found in the *N*-alkylations of structures bearing more than one nitrogen atom is the necessity of using vulnerable nitrogen protecting groups, because of the virtually impossible selective functionalization of these naked groups.[27] Results are pictured in Scheme 1.



Scheme 1

Remarkably, by using only one equivalent of allylating agent in MeTHF/KF–Al_2O_3, functionalization occurred exclusively at the imidic nitrogen, affording exclusively compound **11**, in which the arylamino function remained untouched. (Scheme 1) This experimental observation may be explained on the basis of the higher acidity of the imidic proton (compared to the aminic ones), which is preferentially removed in the presence of a relatively strong base as KF-Alumina.

Interestingly, these results complemented our previous established protocol for the chemoselective KF-Celite promoted aniline allylation.[18] In fact, by using such conditions on the same substrate **10**, we were able to recover a mixture of products, **12** and **13** (Scheme 1), in which the major one (12.5/1) was the derived from the aryl amino moiety. Evidently, the milder basicity of KF-Celite compared to KF–Al_2O_3, did not allow an efficient abstraction of the imidic proton. Remarkably, this result appears to constitute a confirmation of the poor result observed by using KF-Celite in imide functionalization (Table 1), as well a strong evidence of the importance of the support of the inorganic base.

In conclusion, we described a convenient and really valuable method for the *N*-alkylation of phthalimide derivatives promoted by KF-Alumina in the more environmentally friendly green solvent 2-methyltetrahydrofuran (MeTHF). This method offers a series of advantages over classical procedures, including high regio- and enantioselective pathways in the presence of asymmetric bifunctional structures, wide applicability to different electrophiles as well as substituted phthalimide nucleus, and expands the range of organic procedures which can be conducted in MeTHF.

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