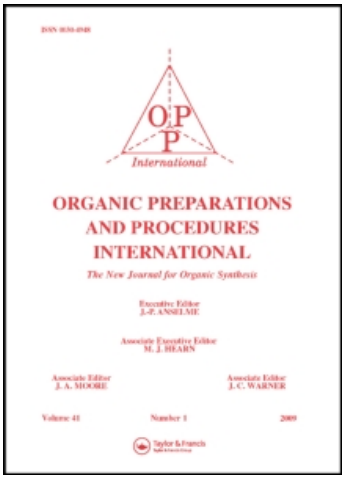

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AN IMPROVED APPROACH TO *N*-SUBSTITUTED MALEIMIDES AND PHTHALIMIDES BY MICROWAVE-PROMOTED MITSUNOBU REACTION

Submitted by (08/18/08)

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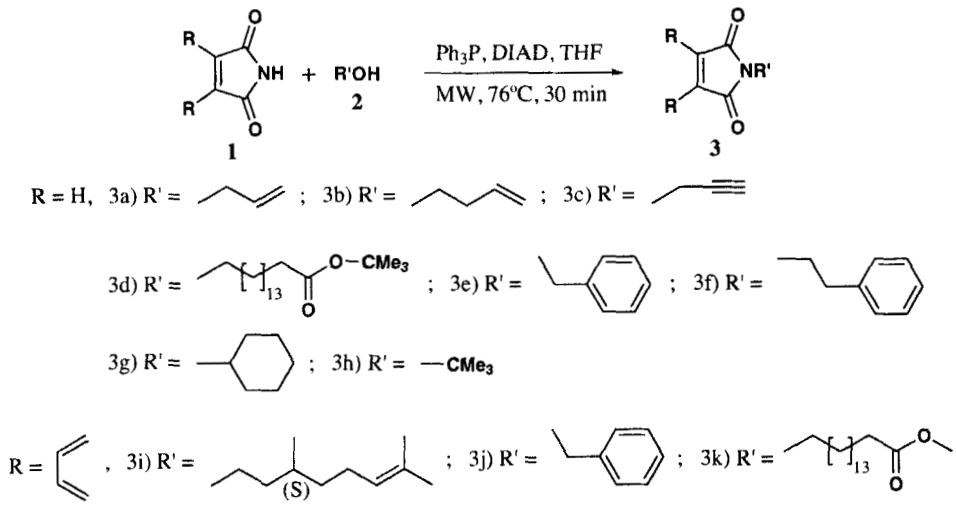
Maleimide derivatives are of high interest as substrates in biological applications. Due to its Michael-accepting ability the maleimido group is able to react with nucleophilic groups, *e. g.* thiol groups in biomolecules.[1] Therefore substrates containing terminal maleimido functionality can undergo covalent coupling to cysteine residues of enzymes or other proteins.[2] Bifunctional derivatives with a maleimido group attached to one end and a connectable functionality on the opposite end can be used for cross-linking proteins.[3,4] Maleimides are widely used as dienophiles with a variety of dienes in Diels-Alder-type cycloaddition reactions.[5,6]

In literature only few methods for the synthesis of *N*-substituted maleimides are described. A commonly used method is the reaction of an amine with maleic anhydride followed by dehydration.[7-9] However, this procedure is limited to amines which are stable to the dehydration conditions.[10] *N*-Substituted phthalimides, which can serve as a protecting group for the amino group, are conveniently prepared by reaction of potassium phthalimide with alkyl halides, in the first step of the Gabriel synthesis.[11] Alternatively, direct *N*-alkylation of maleimides and phthalimides can be accomplished by the Mitsunobu reaction, using alcohols as the alkyl group donors.[12] The activating agents in the Mitsunobu protocol are triphenylphosphine and azodicar-

boxylates such as diisopropyl azodicarboxylate (DIAD). The major advantages are the mild reaction conditions that avoid the use of strongly acidic or basic reagents (*Scheme 1*).



Scheme 1

Because of these benefits and the need of preparing a number of *N*-alkylimides, we selected this protocol. However, as the standard reported Mitsunobu conditions[18] did not give satisfactory results in all cases, we sought to optimize the reaction conditions. We focused on microwave chemistry,[13] which exhibits several benefits such as reduced reaction times, increased yields and energy-efficient as well as clean reaction profiles.[14,15] Despite this, there are only few reports in the literature on microwave-promoted Mitsunobu reactions. Those few reports described reactions under extreme microwave conditions, *e. g.* high reaction temperatures and high pressures.[16,17] So far, there is no report on a microwave-promoted Mitsunobu-type synthesis of *N*-substituted maleimides.

Here we describe a microwave application under mild conditions for the synthesis of *N*-substituted maleimides and phthalimides. Standard conditions for a conventional Mitsunobu synthesis of these imides require stirring for about 24 h at room temperature and result in low to moderate yields.[18] In contrast, our selected microwave conditions gave increased yields in all cases except for compound **3f** (*Table 1*). The primary alkyl maleimides **3a-c** could be obtained in high yields (65-85%). While the *N*-alkyl maleimide **3d** containing a long chain alkanoic ester could not be obtained under conventional conditions, our microwave method led to a yield of 51%.

Walker previously reported on a modified conventional Mitsunobu procedure wherein the order of addition of reactants, the addition of a "non-reacting" alcohol (*e. g.* neopentyl alcohol), and a starting reaction temperature of –78°C was claimed to be essential for obtaining the products in reasonable yields.[19] By using this modified Mitsunobu method, Walker obtained *N*-benzylmaleimide (**3e**) in 87% yield vs. 73% employing standard conditions.[18] As is shown in

Table 1. Yields, mp., Mass and ^{13}C NMR Spectral Data

Cmpd.	Yield (%) microwave irradiation ("conventional")	Physical condition; mp. in °C (*lit.* mp.)	HR-MS (m/z): Calculated. Found	^{13}C NMR (δ, $CDCl_3$)
3a	85 (75[a])	White solid 43 (42-44[a])	137.0477. 137.0478 [EI, M^+]	170.2 (2 C, CO), 134.1 (2 C, CH), 131.5 (CH_2), 117.6 (CH), 39.9 (CH_2)
3b	79 (77[b])	Colorless oil	151.0633. 151.0615 [EI, M^+]	170.8 (2 C, CO), 134.4 (CH_2), 134.0 (2 C, CH), 117.6 (CH), 37.2 (CH_2), 32.9 (CH_2)
3c	65 (n.i.[c,d])	Pale yellow oil	149.0477. 149.0470 [EI, M^+]	170.9 (2 C, CO), 134.1 (2 C, CH), 80.0 (quart. C), 70.3 (CH), 36.3 (CH_2), 18.3 (CH_2)
3d	51 (0[e,f])	White solid	51.0-52.3 408.3108. 408.3111 [ESI, M+H]$^+$	173.4 (CO), 170.9 (CO), 134.0 (2C, 79.9 (quart. C), 38.0 (CH_2), 35.6 (CH_2), 29.6-29.1 (10 C, CH_2), 28.6 (CH_2), 28.1 (CH_3), 26.8 (CH_2), 25.1 (CH_2)
3e	90 (87[g], 73[a])	White solid 67-68 (69-70[g])	187.0627. 187.0627 [EI, M^+]	171.4 (2 C, CO), 137.3 (quart. C), 135.3 (2 C, CH), 129.1 (2 C, CH), 128.8 (CH), 127.7 (2 C, CH), 41.0 (CH_2)
3f	79 (52[a], 90[g])	White solid 110 (112[a])	201.0790. 201.0790 [EI, M^+]	170.8 (2 C, CO), 138.1 (quart. C), 134.4 (2 C, CH), 128.6 (2 C, CH), 128.4 (2 C, CH), 126.4 (CH), 38.4 (CH_2), 33.7 (CH_2)
3g	21 (14[f])	White solid 87-89 (92-94[h])	179.0946. 179.0941 [EI, M^+]	170.9 (2 C, CO), 133.9 (2 C, CH), 50.7 (CH), 29.9 (2 C, CH_2), 26.0 (2 C, CH_2), 25.0 (CH)
3h	0 ([d])	N/A	N/A	N/A
3i	98 (67[f], 37[i])	Colorless oil	285.1729. 285.1731 [EI, M^+]	168.4 (2 C, CO), 133.8 (2 C, CH), 132.5 (2 C, CH), 131.3 (quart. C), 124.5 (CH), 123.1 (2 C, CH), 36.7 (CH_2), 36.3 (CH_2), 35.4 (CH_2), 30.3 (CH), 25.7 (CH_3), 25.3 (CH_2), 19.3 (CH_3), 17.6 (CH_3)
3j	89 (57[j])	White solid 115 (114-115[j])	237.0790. 237.0789 [EI, M^+]	167.7 (2 C, CO), 136.7 (quart. C), 134.6 (2 C, CH), 131.6 (2 C, CH), 128.6 (2 C, CH), 127.4 (CH), 127.3 (2 C, CH), 123.3 (2 C, CH), 40.8 (CH_2)
3k	85 ([k])	White Solid 76.2-77.2 ([k])	415.2723. 415.2747 [EI, M^+]	174.5 (CO), 168.7 (2C, CO), 134.2 (2 C, CH), 132.7 (2 C, quart. C), 123.3 (2 C, CH), 51.6 (CH_3), 38.4 (CH_2), 34.4 (CH_2), 30.1-29.5 (10 C, CH_2), 29.0 (CH_2), 27.3 (CH_2), 25.4 (CH_2)

a) Ref. 18. b) Ref. 6. c) Ref. 21 d) not investigated. e) *Anal.* Calcd. for $C_{24}H_{41}NO_4$: C, 70.72; H, 10.14; N, 3.44. Found: C, 70.79; H, 10.37; N, 3.42. f) performed under standard conditions according to ref. 18: rt, 24 h. g) Ref. 19. h) Ref. 9 i) Ref. 22. j) Ref. 20. k) Ref. 23, no m.p. and yield indicated.

the present work using the microwave-promoted procedure to the synthesis of *N*-benzylmaleimide (**3e**), the order of addition of the reagents is not of outstanding importance. Furthermore, a non-reacting alcohol-additive is not necessary to obtain good yields. Compared to Walker's modified Mitsunobu procedure, the synthesis of *N*-benzylmaleimide (**3e**) can be easily performed with a significantly reduced reaction time under microwave conditions, which results in an increased product yield of 90%. Even the secondary alkyl maleimide **3g**, which has not been synthesized so far by using the Mitsunobu protocol,[10] can be obtained in a moderate yield by using our method. As expected, the *N*-tert butyl compound **3h** was not obtained.

The synthesis of the phthalimide compounds **3i-k** could be carried out in an analogous manner and the products were obtained in high yields as well. For the synthesis of compound **3j** a further modification of the conventional Mitsunobu reaction using a polymer-supported alkyl azodicarboxylate instead of DIAD has been described in literature, which gave a yield of only 57%.[20]

In summary, we have developed a new microwave-promoted method for the synthesis of *N*-substituted maleimides and phthalimides bearing primary and secondary alkyl groups in moderate to high yields. Compared to the conventional procedures, the advantages are short reaction times, easy reaction set-up and increased product yields.

EXPERIMENTAL SECTION

All solvents were of HPLC or p.a. grade, if not they were distilled before use. All chemicals were purchased from Sigma Aldrich (Schnelldorf, Germany) and Acros Organics (Geel, Belgium). Reactions were monitored by TLC using pre-coated plastic sheets POLYGRAM® SIL G/UV254 from Macherey-Nagel (Düren, Germany). Silica gel 60 (particle size 0.040-0.063 or 0.015 - 0.040 mm) from Merck (Darmstadt, Germany) was used for silica column chromatography (SCC). NMR spectra were recorded on JEOL Eclipse plus NMR workstations (Jeol GSX 400 or JNMR GX 500 instrument) with TMS as internal standard. Electron Impact High Resolution Mass Spectra (EI-HRMS) were recorded on a GC Mate II Jeol. Electrospray Ionization High Resolution Mass Spectra (ESI-HRMS) were recorded on Thermo Finnigan LTQ FT (Thermo Finnigan, Bremen, Germany). Elemental analyses were performed on a CHN-Analyser Rapid (Heraeus). IR spectra were obtained on a Perkin Elmer Paragon 1000 spectrometer. Melting points were determined on a Büchi 540 apparatus (Büchi, Flavil, Switzerland). The laboratory microwave Discover™ was from CEM (Kamp-Lintfort, Germany). All new products were characterized by mp., ^{1}H NMR, ^{13}C NMR, HR-MS, IR and elemental analysis. The spectroscopic data of known products were in agreement with those published in the literature.

Typical Procedure.- In a 100 mL round bottom flask, triphenylphosphine (3.16 mmol) and the imide (3.16 mmol) were dissolved in anhydrous THF (12.6 mL). The corresponding primary or secondary alcohol (1.56 mmol) and DIAD (3.16 mmol) were added, and the open flask was placed in a single-mode microwave reactor (Discover, CEM GmbH) and fitted with a reflux condenser. Microwave irradiation was performed at a maximum output of 50 W and a maximum temperature of 76°C over a reaction time of 30 min with stirring after a heating-ramp of 5 minutes. Temperature was measured with an IR-sensor. After removal of the solvent, the product

was purified by silica column chromatography (silica gel 60, 4:1 hexane/ethyl acetate) to yield the *N*-alkylimide.

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A NOVEL ACCESS TO SOME 1,4-DICHLOROISOQUINOLINES FROM PHENACYL AZIDES

Submitted by (11/01/07)

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The Vilsmeier-Haack reaction initially used for the formylation of activated aromatic substrates[1] and carbonyl compounds[2] has now evolved into a powerful synthetic tool for the construction of many heterocyclic compounds[3] such as quinolines, indoles, quinazolines, pyridines, etc. In continuation of our previous work on exploring the use of *bis*(trichloromethyl) carbonate (BTC) in organic synthesis,[4] we focused our research on the use of Vilsmeier salts derived from BTC and N,N-dimethylformamide (DMF).[5] Herein we describe a mild and efficient one-step synthesis of substituted 1,4-dichloroisoquinolines and 5-aryloxazole-4-carboxaldehydes from various phenacyl azides under Vilsmeier conditions.