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Solvent Free N-Alkyl and N-Arylimides Preparation from Anhydrides Catalyzed by $TaCl_5$-Silica gel

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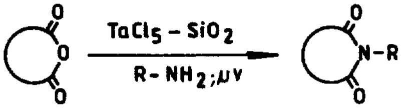
Abstract : The first Lewis acid catalyzed and solvent free procedure for the preparation of imides from the corresponding anhydrides is described involving $TaCl_5$-silica gel as Lewis acid under microwave irradiation. © 1997 Elsevier Science Ltd.

Imide derivatives are associated with various uses both in biology[1] and synthetic chemistry[2]. For example, maleimides are important constituents of peptide-conjugate haptens[3], antibody-antibody conjugates[4], immuno conjugates[5], enzyme inhibitors and enzyme probes[6]. Also these are good Michael acceptors and Diels-Alder dienophiles[7]. It is not surprising therefore, that preparation procedures for these compounds are in great demand. The popular procedures include-dehydrative condensation of an anhydride and amine at high temperature and cyclization of amic acid intermediates in presence of acidic reagents[8]. The direct N-alkylation of imides with alcohols under Mitsunobu reaction conditions is yet another popular method[9]. The recent addition to these has been a Lewis acid-hexamethyl disilazane protocol wherein stoichiometric amounts of these reagents have been used[10]. However many of these have short comings, such as poor yields, carcinogenic solvent media, and stoichiometric reagent requirement. To address all these limitations, we report herein, for the first time, a solvent free, $TaCl_5$-silica gel[11] catalyzed imide synthesis under microwave irradiation (eq.1). Incidentally, this constitutes the first catalyzed and base free reaction for preparing this class of compounds. The conceptual reasoning for this has been the high oxophilicity of $TaCl_5$, the affinity of activated silica gel as water scavenger and rapid heating capacity of microwave oven.

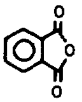
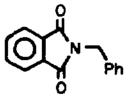
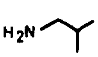
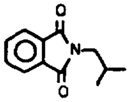
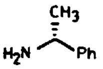
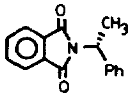
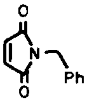
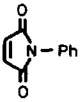
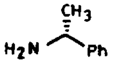
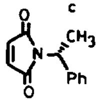
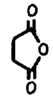
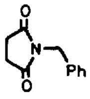
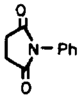
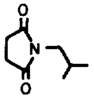
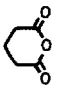
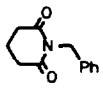


Eq. 1

IICT Communication No. 3856

When equimolar phthalic anhydride (table 1, entry 1) and benzylamine were adsorbed on silica gel, admixed with 10 mole percent of $TaCl_5$-SiO_2 and exposed to microwave irradiation for 5 minutes, a short silica column eluting with CH_2Cl_2 generated the N-benzyl phthalimide in 92% isolated yield.

Table 1: Synthesis of N-Alkyl and N-Arylimides.

ENTRY	ANHYDRIDE	AMINE	AMIDE	TIME (MIN)	YIELD (%)[a]
1				5	92
2				5	90
3			 [b]	5	88
4				5	82
5		H_2N-Ph		6	79
6			 [c]	5	78
7				6	80
8		H_2N-Ph		6	75
9				6	78
10				7	74

a) Yields based on isolation of chromatographically homogeneous products. b) $[\alpha]_D$ *+60.4(c 1.0* $CHCl_3$*). c) Ref. 12*

The versatality of this procedure is illustrated using isobutylamine (entry 2) and R(+)-α-methylbenzylamine (entry 3). This solvent free reaction procedure has proved to be superior for the preparation of maleimide derivatives as well. For instance, maleic anhydride on treatment with bezylamine (entry 4) yielded N-benzyl maleimide in 82% yield. Similar results were observed with aniline (entry 5) and R(+)-α-methylbenzylamine (entry 6). The mildness of the experimental procedure has been established by comparing the optical rotation of product of entry 6 $[\alpha]_D$+68.4°(c 1.0, $CHCl_3$) [lit[12] $[\alpha]_D$-69.25°(neat)]. Otherwise less reactive succinic anhydride and glutaric anhydride were converted to corresponding succinimides (entries 7,8 and 9) and glutarimide (entry 10) respectively.

The results from all these experiments[13] prove that the $TaCl_5$-silica gel acted as a very efficient Lewis acid catalyst under microwave assistance. Also, the avoiding of carcinogenic solvents, high yields and shorter reaction times, undoubtedly offer many advantages over existing procedures. The usefulness of this new combination - $TaCl_5$-SiO_2-microwave is currently being extended to some other Lewis acid assisted reactions.

General procedure for the synthesis of imide derivatives (entries 1-10) : N-Benzyl phthalimide (entry 1).

Phthalic anhydride (0.36g, 2.4 mmol) and benzylamine (0.27 ml, 2.4 mmol) were adsorbed on activated silica gel (100-200 mesh, dried overnight at 100°C) and stirred at room temperature for 1 h under inert atmosphere. To this was added $TaCl_5$-SiO_2 (0.37 g, 10 mole percent) and admixed thoroughly and irradiated in a microwave oven (448 watts) for 5 min. The mixture was cooled to room temperature, charged on a small silica pad and eluted with CH_2Cl_2 (30 ml). Removal of volatiles furnished N-benzyl phthalimide (0.53 g, 92%).

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11. The tantalum (V) chloride - silica gel was prepared by mechanically shaking chromatography grade silica gel (10g, 100-200 mesh, dried over night at 100°C) and tantalum (V) chloride (3g) for 20h. The overnight drying of silica gel is not essential, however it is advisable to make sure silica gel to be anhydrous for optimal yields. The thorough admixing $TaCl_5$-silica gel is critical.
12. Doichi, T.; Yamaguchi, H. *Eur. Polym. J.* **1984**, *20*, 831 ; S(-)-α-methylbenzylamine has been used in this report.
13. All compounds were characterized by ^1H NMR, IR and mass spectroscopy.

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