Solid Phase-Solid State Synthesis of N-alkyl Imides from Anhydrides[#]

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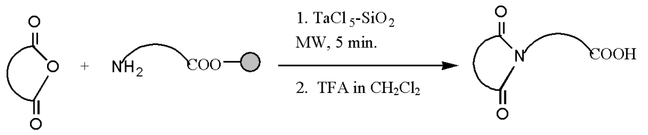
Abstract: Preparation of N-alkyl imides from anhydrides is developed on polymer support in solid state assisted by microwave for the first time.

Key words: solid phase, solid state, microwave, trifluoroacetic acid



Solvent free approach for organic functional group transformations has gained prominence recently.[1] This approach has several added advantages *viz.*, i) The environmental hazards through use of solvents is minimized, ii) The microwave[2] heating which has become a powerful alternative for thermal reactions demands solvent free conditions in several cases. The substrate bound Resins in few cases may not tolerate many solvents due to swelling properties.[3] To address all these issues a judicious programme is initiated by us wherein solvent free reaction conditions have been developed for N-alkyl imide synthesis[4] and 1,3-diol preparation.[5] Further to this, some organic functional groups have been reduced on solid phase (Merrifield Resin as support) wherein no solvent was used as reaction media.[6]

Our continued interest in developing new protocols in solid supported organic synthesis has prompted us to study the preparation of N-phthalimides and derivatives from anhydrides on solid phase (Merrifield Resin) under solvent free conditions. It is important to note that this reaction needs Lewis acid catalyst adsorbed on silica gel and heating is essential. Herein we report our latest findings. Interestingly, this paper describes for the first time two insoluble supports namely Merrifield's Resin and Silica gel usage in one pot which are easily separated physically by using different mesh filters.[7] To assess the scope of this methodology, γ-aminobutyric acid was esterified with Merrifield Resin,[8] treated with phthalic anhydride and TaCl$_5$-SiO$_2$ [9] (*vide infra*), and subjected to microwave irradiation after thorough mixing. The solid mixture was washed with DMF (2x20 mL), MeOH (2x20 mL), H$_2$O (2x10 mL) diethyl ether (2x20 mL) CH$_2$Cl$_2$ (2x20 mL). The resultant polymer bound imide is cleaved from resin by treatment with trifluoroacetic acid to furnish acid derivative of **1b** (entry 1) in 65% yield.

General Equation

This result has encouraged us to study some other substrates wherein polymer supported γ-amino butyric acid ester is treated with maleic anhydride[10] **2a** (entry 2) and succinic anhydride **3a** (entry 3). Good conversion to imides was obtained. Similar results were observed by the use of polymer supported alanine with phthalic anhydride[10] **4a** (entry 4), maleic anhydride **5a** (entry 5). and succinic anhydride **6a** (entry 6)

This study has provided further evidence in confirming our hypothesis that Solid Phase-Solid State functional group transformations can be accomplished in the absence of solvents and assisted by microwave heating. The imide derivatives thus synthesized constitute the important skeleton of antibody-antibody conjugates, enzyme inhibitors and enzyme probes.[11]

General procedure for the preparation of N-alkyl imides: 4-(1,3-2,3-dihydro-1*H*-2isoidolyl)butanoic acid 1b:

The polymer bound γ-amino butyric acid (1.078g, 1mmol) entry 1 phthalic anhydride (0.185g, 1.25mmol) and activated Silica gel (1g) were thoroughly mixed and to this was added TaCl$_5$-SiO$_2$(0.169g, 10mole percent) and admixed thoroughly and subjected to microwave irradiation[12] (450watts) for 5min and the solid mixture was allowed to cool to room temperature and the organic material is cleaved from resultant resin-silica gel mixture using TFA (3mL) in CH$_2$Cl$_2$ (10mL) (2x10mL) and the combined filtrates were evaporated to yield acid derivative of **1b** (0.189g, 65%).

Yield: ^{1}H NMR (CDCl$_3$) : 7.8-7.9 (m, 2H), 7.65-7.75 (m, 2H), 3.7-3.9 (t, 2H), 2.35-2.45 (t ,2H), 1.09-2.05 (m, 2H); MS: (m/z)233 (M$^+$); HRMS: Calculated 233.0688, Found 233.0692.

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References and Notes

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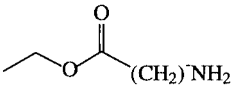
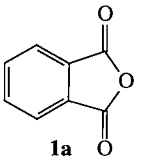
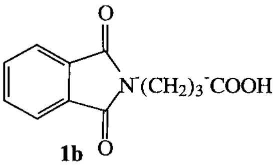
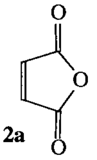
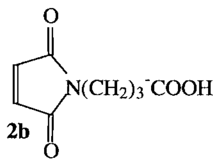
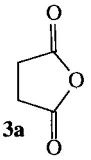
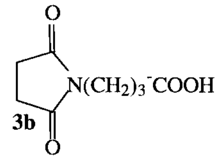
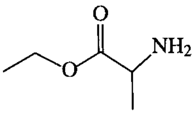
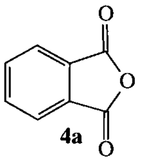
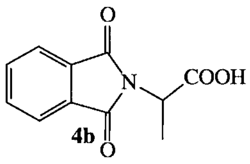
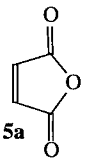
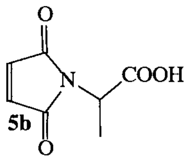
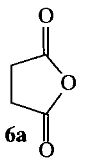
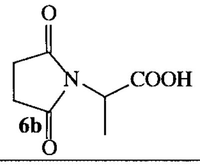
Table 1 Synthesis of N-alkylimide on Solid Support in Solid State

Entry	Polymer bound amine	Anhydride	Imide*	Time min.	Yield %**
1.		 **1a**	 **1b**	5	65
2.	"	 **2a**	 **2b**	5	65
3.	"	 **3a**	 **3b**	7	60
4.		 **4a**	 **4b**	5	72
5.	"	 **5a**	 **5b**	5	60
6.	"	 **6a**	 **6b**	6	58

* The imide is obtained after cleavage from polymer using TFA (See Experimental)
** Yields are based on isolation of corresponding acid after cleavage by TFA
= Polymer (chloromethyl polystyrene)

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(7) The mesh filter is not very efficient in separation of silica gel (finer than 200 mesh) and resin (≈150μ) is used. However, by use of resin with more than 300μ (commercially available from polymer laboratories, USA) should enable easy separation. In the present instance Merrifield resin (150-300μ) is used.

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(10) Refluxed in benzene for 8h followed by standard workup and cleavage afforded the corresponding acids in less than 30% yield.

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(12) *BPL SANYO* (600 watts) domestic microwave was used with an output at 75% for 5 minutes (after each minute, the reaction mixture is thoroughly agitated).

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