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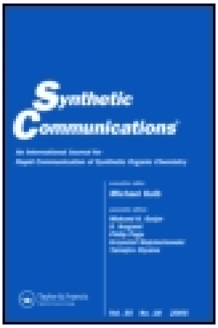

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Microwave Assisted, Highly Efficient Solid state N- and S-Alkylation

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SYNTHETIC COMMUNICATIONS, 29(21), 3693–3698 (1999)

MICROWAVE ASSISTED, HIGHLY EFFICIENT SOLID STATE N- AND S-ALKYLATION

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Abstract: Secondary amines and thiophenols were alkylated with alkyl and benzyl halides rapidly on alumina supported potassium carbonate under solvent-free conditions using microwaves. Equimolar amounts of the secondary amine/thiophenol and alkyl halide were used. The procedure neither required any strong base nor a PTC. Aniline was also monobenzylated with benzylchloride. Separation of the products from the reactants was very simple by using a nonpolar solvent for desorption.

Solid inorganic supports are being increasingly used in synthetic organic chemistry.[1-2] Their effectiveness in organic synthesis may be due to their large surface area, the presence of pores, and the suitable adsorption of the reactants on their surface. Reactions on such supports often involve milder conditions, easier work-up, and higher selectivity than the reactions in the solution phase.

Microwave heating has already gained importance in synthetic organic chemistry in a short span of only a decade.[3-5] However the use of solvents in MW ovens

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gives rise to elevated temperatures and consequently high pressures. These problems have been overcome to a large extent by carrying out the reactions in the modified oven or under 'dry' conditions using solid supports. MW enhanced chemical reactions on inorganic solid supports under solventless conditions have attracted attention recently.[6-7] The advantages of this method are enhanced reaction rates, less or no formation of side products and higher yields of pure products.

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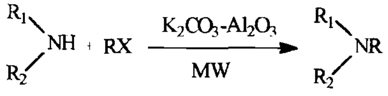
N-alkylation of secondary amines with alkyl halides is an important synthetic method to obtain tertiary amines. However, quaternary salt formation results in lower yields of the tertiary amines. Generally a large excess of the secondary amine is used to control this.[8] Use of strong bases like lithium naphthalenide,[9] Et_3N & KH,[10] KOH in acetone[11] and in DMSO[12] have been made. Some phase transfer catalysts have also been employed to improve the yields.[13-14] KF on alumina is reported for N-alkylation.[15] N-benzylaniline is prepared by using a molar ratio of 4:1 of aniline: benzyl chloride. The reaction is carried out for 4 h at 90-95°c in the presence of K_2CO_3.[16] Arylpiperazines are alkylated using K_2CO_3 as the base in a solvent. The reported reaction time is 16h.[17] There are a few reports on N-alkylation of amines under MW irradiation. Benzoxazinones and benzothiazinones have been N-alkylated using sodium ethoxide as a base, triethylbenzylammonium chloride as a phase transfer catalyst and silica gel as support.[18] The other reports are of N-alkylation of Carbazole with alkyl halide adsorbed on K_2CO_3,[19] aza heterocycles in dry media,[20] triazole and benzotriazole in basic media,[21] and azoles in dry media.[22] N-alkylation of arylpiperazines and that of aniline is not reported under MW irradiation.



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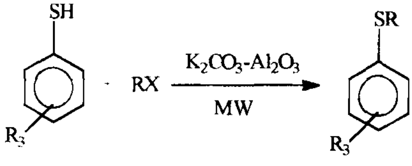

II

Table

Yields of alkylated products under optimized conditions

Substrate	**Alkyl halide**	**Irradiation time (mins.) / Power (%)**	**Yield (%)**[a]
Phenylpiperazine	$BrCH_2CN$	5 / 50	70
Phenylpiperazine	$BrCH_2CH(OEt)_2$	5 / 50	50[b]
Phenylpiperazine	$BrCH_2Ph$	5 / 50	74
o-Tolylpiperazine	$Cl(CH_2)_3CH_3$	25 / 10	50
o-Tolylpiperazine	$2\text{-}ClC_6H_4CH_2Cl$	8 / 40	77[c]
Pyrrolidine	$BrCH_2Ph$	13 / 20	98
Benzimidazole	$ClCH_2Ph$	8 / 40	43
Thiophenol	$BrCH_2Ph$	5 / 50	98
Thiophenol	$BrCH_2CH_2CH_3$	13 / 20	72
p-Chlorothiophenol	$Cl(CH_2)_3CH_3$	13 / 20	70
Aniline[d]	$ClCH_2Ph$	2 / 50	67

[a] The products obtained exhibited satisfactory physical and spectral data.

[b] PMR ($CDCl_3$): δ (ppm):- 1.25 (t, 6H, $-CH_3$ of acetal group), 2.6 (d, 2H, $-CH_2-$ attached to piperazine ring), 2.7 (t, 4H, piperazine ring protons), 3.2 (t, 4H, piperazine ring protons), 3.6 (q, 2H, $-CH_2-$ of acetal group), 3.7 (q, 2H, $-CH_2-$ of acetal group), 4.7 (t, 1H, -CH- attached to $-CH_2-$), 6.8-7.2 (m, 5H, aromatic ring protons)

[c] PMR ($CDCl_3$): δ (ppm):- 2.3 (s, 3H), 2.7 (t, 4H, piperazine ring protons), 3.0 (t, 4H, piperazine ring protons), 3.7 (s, 2H), 7.0-7.6 (m, 7H, aromatic ring protons)

[d] Molar ratio of Aniline: Benzylchloride, 4:1; The product was purified through a short column of silica gel (mesh size 60-120) using toluene as the eluent.

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Conventionally thioethers are formed by alkylation of the thiolate anions with alkyl halides in an inert atmosphere.[23] KOH in DMSO,[24] phase transfer catalysts,[25-26] DBU,[27] K_2CO_3-DMF[28] and NaX zeolites[29] have been used. Bulman Page et al. have reported the use of Na2CO3 and a catalytic amount of (dppm)$PtCl_2$ [dppm=bis (diphenylphosphinomethane)].[30] Refluxing thiophenols and alkyl halides with K_2CO_3-Al_2O_3 in benzene is reported to give 65-87% thioethers.[31] Use of n-BuLi is also reported.[32] There are no reports of S-alkylation under MW irradiation.

We report here an easy method of alkylation of secondary amines, thiophenols and monoalkylation of aniline using K_2CO_3 on alumina as support under MW irradiation. The starting materials were separately adsorbed on the support as simultaneous adsorption resulted in the formation of a quaternary salt as the major product. Good yields of pure alkylated products were obtained by simple desorption with a non-polar solvent. The method reported here does not require any strong base or any phase transfer catalyst.

General Procedure: 5 mmol of K_2CO_3 i.e. 0.69 g was coground with 12 g of alumina in an agate mortar. To 5mmol of the secondary amine/thiophenol in 10 ml Et_2O was added the mixture of K_2CO_3- Al_2O_3. Et_2O was evaporated with stirring to give a dry mixture. 5mmol of alkyl halide in 10 ml Et_2O was added to the above dry mixture. Et_2O was again evaporated with stirring. The resultant dry mixture was irradiated in a beaker covered with a petridish in the MW oven (IFB, output 750 watts) for the specified time. The product was obtained by desorption with toluene.

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