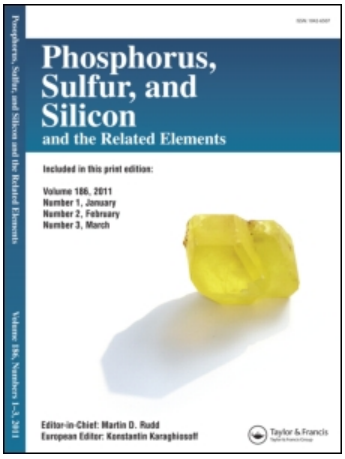

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ORGANIC REACTIONS WITHOUT SOLVENT: MICHAEL ADDITIONS ON AN UNSATURATED SULFONE AND SULFOXIDE

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ORGANIC REACTIONS WITHOUT SOLVENT: MICHAEL ADDITIONS ON AN UNSATURATED SULFONE AND SULFOXIDE

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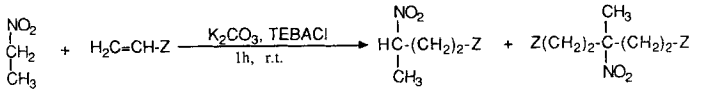
Solid-liquid phase transfer catalysis in the absence of any solvent efficiently promotes Michael additions of nitro alkanes and of diethyl *N*-acetylaminomalonate to phenyl vinyl sulfone and to phenyl vinyl sulfoxide. The adduct of the Michael addition to diethyl *N*-acetylaminomalonate to phenyl vinyl sulfoxide was converted by distillation under partial vacuum to diethyl *N*-acetylamino vinyl malonate which gave (±)-vinylglycine by hydrochloric acid catalysis.

Key words: Michael addition; sulfone; sulfoxide; phase transfer catalysis; amino acids.

Vinyl sulfones and vinyl sulfoxides have been extensively used as dienophiles[1] and Michael acceptors[2] due to the synthetic utility of sulfinyl and sulfonyl groups.[3] in particular, Michael addition to aryl vinyl sulfoxides followed by thermolysis of the resulting adduct is a commonly used process for introducing a vinyl group to a nucleophilic center.[4,5]

Michael addition of carbanions to α,β-unsaturated sulfones is normally achieved by using sodium hydride[6] as a basic catalyst. Potassium fluoride in the presence of alkaloidonium salts has also been proposed.[7] The Michael addition of carbanions to conjugated sulfoxides is more difficult than to the corresponding sulfones. Sodium hydride,[8] sodium ethoxide,[9] and potassium *tert*butoxide[4] have, therefore, been used but in a comparative study,[10] 1,8-diazabicyclo[5.5.0]undec-7-ene (DBU) was shown to be the most efficient basic catalyst.

We have recently used solid-liquid phase transfer catalysis (PTC) in the absence of any organic solvent to achieve Michael additions of hindered carbanions to enones.[11,12] We report here the application of this process to the condensation of carbanions generated from nitroalkanes, namely nitroethane **1a** and 2-nitropropane **1b** and from diethyl N-acetylaminomalonate **1c** to phenyl vinyl sulfone **2a** and to phenyl vinyl sulfoxide **2b**. Under our conditions, Michael donors **1** were reacted with acceptors **2** in the presence of K_2CO_3 and benzyltriethylammonium chloride (TEBACl); final products were isolated by



1a **2** **3** **4**

2a: Z= $SO_2C_6H_5$
2b: Z= SOC_6H_5

SCHEME 1

extraction of the reaction mixture with methylene chloride at the end of the process.

The conjugate additions of nitroethane **1a** to acceptors **2** can lead to monoalkylated products **3** or dialkylated products **4** (Scheme 1) according to reaction conditions (Table I).

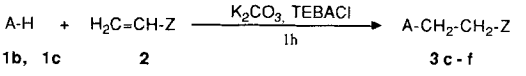
TABLE I

Reaction of acceptors **2** (10 mmol) with variable amounts of nitroethane in the presence of variable amounts of K_2CO_3 and of TEBACl (0.5 mmol).

1a (mmol)	**2**	K_2CO_3 (mmol)	**3** (yield %)	**4** (yield %)
10	**2a**	0.5	**3a** (0)	**4a** (96)
10	**2b**	0.5	**3b** (0)	**4b** (92)
50	**2a**	0.5	**3a** (63)	**4a** (21)
50	**2b**	0.5	**3b** (67)	**4b** (18)
50	**2a**	10	**3a** (73)	**4a** (18)
50	**2b**	10	**3b** (81)	**4b** (8)

Monoalkylated products were formed only when excess of nitroethane was used. Raising the quantity of base also slightly improved the yield of formation of monoalkylated compounds **3**. Interpretation can be made in terms of acid strengthening resulting from the substitution of an hydrogen by an alkyl group α to a nitro group.[13]

The addition of 2-nitropropane **1b** to acceptors **2** took place readily at room temperature. The reaction of diethyl N-acetylaminomalonate **1c** with phenyl vinyl sulfone **2a** could be achieved at room temperature but, the yield of the reaction of **1c** with phenyl vinyl sulfoxide was improved when the reaction was performed at 60°C (Scheme 2, Table II).



1b, 1c **2** **3c-f**

1b A-H= H-$C(CH_3)_2NO_2$
1c A-H= H-$C(COOEt)_2NHCOCH_3$

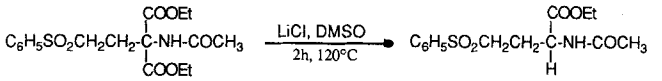
SCHEME 2

Adducts **3e** and **3f** are precursors for the synthesis of amino-acids. Heating **3e** in DMSO under Krapcho[14] conditions furnished the decarboxylated derivative **5** (Scheme 3).

TABLE II

Reaction of equimolecular amounts (10 mmol) of donors **1b**, **1c**, and acceptors **2a**, **2b** in the presence of K_2CO_3 (0.5 mmol) and TEBACl (0.5 mmol).

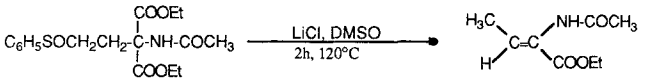
1	2	reaction temperature (°C)	3	(Yield %)
1b	**2a**	20	**3c**	(86)
1b	**2b**	20	**3d**	(98)
1c	**2a**	20	**3e**	(81)
1c	**2b**	20	**3f**	(38)
1c	**2b**	60	**3f**	(97)



3e 5

SCHEME 3

Under the same conditions, **3f** led to ethyl 2-acetylamino-2-butenoate **6** (Scheme 4).

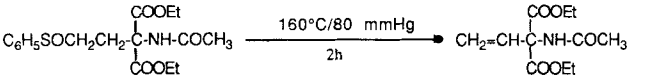


3f 6

SCHEME 4

This result can be explained by the mechanism of thermal decarboxylation in DMSO, which involves a carbanionic intermediate giving rise to the migration of the double bond.

The elimination of the sulfinyl group could be achieved by heating at 160°C under partial vacuum leading to diethyl *N*-acetylamino vinyl malonate **7** (Scheme 5)



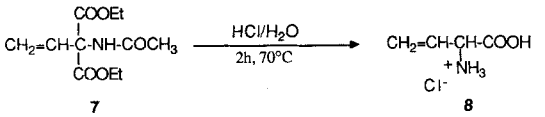
3f 7

SCHEME 5

Diethyl N-acetylamino vinyl malonate **7** is a useful intermediate in the synthesis of vinylglycine.[15,16] Diethyl N-acetylamino vinyl malonate has been previously obtained either by Michael addition of diethyl *N*-acetylaminomalonate **1c** on phenyl-2-(trimethylsilyl)ethynylsulfone followed by reduction of the adduct with aluminium amalgam[16] or by condensation of **1c** with ethylene using triethylamine and $PdCl_2(CH_3CN)_2$ as catalyst.[17]

Heating **7** in DMSO under Krapcho conditions led to ethyl 2-acetylamino-2-butenoate (Z) **6**.

Diethyl N-acetylamino vinyl malonate **7** was converted to (±) vinylglycine hydrochloride by hydrocholoric acid hydrolysis using a classical method[17] (Scheme 6).



7 8

SCHEME 6

In conclusion, solid-liquid phase transfer catalysis without added solvent appears, at least in the case of the studied examples, more efficient than previously known methods. For instance, a complete addition of 2-nitropropane on phenyl vinyl sulfoxide[18] was obtained in one hour instead of 24 hours when DBU was used, under milder conditions with only a catalytic amount of base, whereas an equimolecular quantity of DBU was needed.[10] This may enhance the interest of phenyl vinyl sulfoxide as (vinyl) cation synthon.

EXPERIMENTAL PART

General procedure for Michael addition. All solid reagents were finely ground. A mixture of Michael acceptor (10 mmol), donor (amount, see tables), K_2CO_3 (amount, see tables) and catalyst: TEBACl (0.13 g, 0.5 mmol) was vigorously shaken at the requisite temperature (see tables) for one hour. After eventual cooling, methylene chloride 20 ml and silica 3 g (which strongly retains the catalyst) were added; after 5 minutes stirring the mixture was filtered and the solids were washed twice with 5 ml methylene chloride. The organic extracts were combined and concentrated in vacuo.

3-*Nitro*-1-(*phenylsulfonyl*)-*butane* **3a**. Was separated from **4a** by column chromatography (silica gel, toluene-ethyl acetate 7:3); Mp 60–62°C, (Lit.[7] 41–41°C); ^{1}H-NMR ($CDCl_3$, δ): 1.50 (d, 3H, CH_3); 2.23 (m, 2H, CH_2CH); 3.10 (t, 2H, CH_2SO_2); 4.64 (m, 1H, CH); 7.48 (t, 2H, aro.); 7.63 (t, 1H, aro.); 7.80 (d, 2H, aro.). $C_{10}H_{13}NO_4S$ (243.28): Calcd.: C, 49.37; H, 5.39; N, 5.73. Found: C, 49.12; H, 5.47; N, 5.65.

3-*Nitro*-1-(*phenylsulfinyl*)-*butane* **3b**. Was separated from **4b** by column chromatography (silica gel, toulene-ethyl acetate 7:3); oil. This product appears to be a mixture (50:50) of diastereoisomers. ^{1}H-NMR ($CDCl_3$, δ): 1.42 and 1.45 (d, 3H, CH_3); 2.16 (m, 2H, CH_2CH); 2.80 (m, 2H, CH_2SO); 4.47 and 4.63 (m, 1H, CH); 7.43 (m, 5H, aro.). $C_{10}H_{13}NO_3S$ (227.28): Cald.: C, 52.85; H, 5.76; N, 6.16. Found: C, 52.65; H, 5.87; N, 6.03.

3-*Methyl*-3-*nitro*-1-(*phenylsulfonyl*))-*butane* **3c**. Was recrystallized from 2-propanol. Mp 96.98°C; ^{1}H-NMR ($CDCl_3$, δ): 1.61 (s, 6H, 2 CH_3); 2.38 (m, 2H, CH_2 CNO_2); 3.12 (m, 2H, Ch_2SO_2); 7.45 (t, 2H, aro.); 7.62 (t, 1H, aro.); 7.87 (d, 2H, aro.). $C_{11}H_{15}NO_4S$ (257.29): Calcd.: C, 51.35; H, 5.87; N, 5.44. Found: C, 51.25; H, 5.75; N, 5.73.

3-*Methyl*-3-*nitro*-1(*phenylsulfinyl*)-*butane* **3d**. Oil; (Lit.[9] no data); ^{1}H-NMR ($CDCl_3$, δ): 1.51 (s, 3H, CH_3), 1.54 (s, 3H, CH_3); 2.28 (m, 2H, CH_2C-NO_2); 2.95 (m, 2H, CH_2SO); 7.39 (s, 5H, aro.). $C_{11}H_{15}NO_3S$ (241.30): Calcd.: C, 54.75; H, 6.26; N, 5.80. Found: C, 54.52; H, 6.03; N, 6.08.

Ethyl 2-*acetylamino*-2-*carbethoxy*-4-(*phenylsulfonyl*)-*butanoate* **3e**. Was recrystallized from 2-propanol; Mp 105–107°C; ^{1}H-NMR ($CDCl_3$, δ): 1.28 (t, 6H, 2 CH_3CH_2); 2.02 (s, 3H, CH_3CO); 2.80 (m, 2H, CH_2CH_2C); 3.18 (m, 2H, CH_2SO_2); 4.22 (q, 4H, 2 CH_2O); 6.80 (s, 1H, NH); 7.48 (t, 2H, aro.); 7.60 (t, 1H, aro.); 7.83 (d, 2H, aro.). $C_{17}H_{23}NO_7S$ (385.40): Calcd.: C, 52.97; H, 6.01; N, 3.63. Found: C, 52.76; H, 5.76; N, 3.85.

Ethyl 2-*acetylamino*-2-*carbethoxy*-4-(*phenylsufinyl*)-*butanoate* **3f**. Was recrystallized from diethyl ether-pantane 50:50; Mp 74–76°C; ^{1}H-NMR ($CDCl_3$, δ): 1.32 (t, 6H, 2 CH_3CH_2); 2.06 (s, 3H, CH_3CO); 2.80 (m, 4H, CH_2CH_2); 4.25 (q, 4H, 2 CH_2O); 6.92 (s, 1H, NH); 7.60 (s, 5H, aro.). $C_{17}H_{23}NO_6S$ (369.41): Calcd.: 55.28; H, 6.26; N, 3.79. Found: C, 55.12; H, 6.35; N, 3.96.

1,5-(*Diphenylsulfonyl*)-3-*methyl*-3-*nitropentane* **4a**. Was recrystallized from ethyl acetate; Mp 182–183°C; ^{1}H-NMR ($CDCl_3$, δ): 1.48 (s, 3H, CH_3); 2.26 (m, 4H, 2 CH_2CH_2C); 2.98 (m, 4H, 2 CH_2SO_2); 7.50 (t, 4H, aro.); 7.62 (t, 2H, aro.); 7.78 (d, 4H, aro.). $C_{18}H_{21}NO_6S_2$ (411.36): Calcd.: C, 52.55; H, 5.13; N, 3.40. Found: 52.46; H, 5.08; N, 3.51.

1,5-(*Diphenylsulfinyl*)-3-*methyl*-3-*nitropentane* **4b**. Was recrystallised from isopropanol; Mp 110–113°C; ^{1}H-NMR($CDCl_3$, δ): 1.45 (s, 3H, CH_3); 2.37 (m, 4H, 2 CH_2CH_2C); 3.04 (m, 4H, 2 CH_2SO); 7.60 (s, 10H, aro.). $C_{18}H_{21}NO_4S_2$ (379.48): Calcd.: C, 56.97; H, 5.57; N, 3.69. Found: C, 56.85; H, 5.49; N, 3.55.

Ethyl 2-*acetylamino*-4-(*phenylsulfonyl*)-*butanoate* **5**. Compound **3e** was decaroxylated using the Krapcho[14] procedure. A mixture of **3e** (7.70 g, 20 mmol) and LiCl (2.1 g, 50 mmol) in DMSO (15 ml) was heated form 2 hours at 120°C. After cooling to room temperature the mixture was poured into water (200 ml) and extracted with ethyl acetate (3 × 10 ml). The organic layer was washed with water, dried and concentrated to 10 ml; **5**, crystallized upon cooling. MP 108–110°C, 5.5 g, 88%. ^{1}H-NMR ($CDCl_3$, δ): 1.12 (t, 3H, CH_3CH_2); 1.76 (s, 3H, CH_3CO); 2.07 (m, 2H, CH_2CH)ff 3.02 (m, 2H, CH_2SO); 4.04 (q, 2H, CH_2O); 4.43 (dxt, 1H, CH); 6.44 (d, 1H, NH); 7.51 (t, 2H, aro.); 7.66 (t, 1H, aro.); 7.80 (d, 2H, aro.). $C_{14}H_{19}NO_5S$ (3.13.36): Calcd.: C, 53.65; H, 6.11; N, 4.47. Found: C, 53.61; H, 6.18; N, 4.31.

Ethyl 2-*acetylamino*-2-*butenoate* (*Z*) **6**. Was prepared by thermolysis in DMSO of compounds **3f** or **7** under the same conditions as, for the preparation of **5** except that **6** could not be recovered by extraction with an organic solvent after dilution with water. The reaction mixture had to be distilled in vacuo; DMSO was first eliminated, then **6** was isolated; bp_2 102–104°C, yielded starting from **3f**: 38%, yield starting from **7**: 62%. ^{1}H-NMR ($CDCl_3$, δ): 1.33 (t, 3H, CH_3CH_2); 1.76 (d, 3H, CH_3CH); 4.22 (q, 2H, CH_2O); 6.76 (q, 1H, CH); 7.30 (s, 1H, NH). $C_8H_{13}NO_3$ (171.19): Calcd.: C, 56.12; H, 7.65; N, 8.18. Found: C, 55.86; H, 7,89; N, 8.39.

Ethyl 2-*acetylamino*-2-*carbethoxy*-3-*butenoate* **7**. In a Claisen flask, **3f** (36.9 g, 100 mmol) was introduced. Partial vacuum (80 mm) was established, and the flash was heated at 160°C for 2 hours. Heating was interrupted and when the mixture had cooled to approximately 80°C reduced pressure was established and **7** was distilled. The distillate contains sulfur byproducts resulting from the elimination of the sulfinyl group. These impurities are usually removed by column chromatography but in this particular case we found it more convenient to cool (−12°C) the distillate overnight. The sulfur derivative which had crystallized as an impurity was removed by filtration and washed with a few ml of pentane. The collected liquids were concentrated in vacuo, furnishing **7** as an oil; $bp_{0.5}$ 125–127°C; (Lit.[16] bp_1 135°C); 21 g, 87%. 1H-NMR ($CDCl_3$, δ): 1.30 (t, 6H, 2 CH_3CH_2); 2.15 (s, 3H, CH_3CO); 4.27 (q, 4H, 2 CH_2O); 5.18 (d, 1H, HC=CH_2); 5.24 (d, 1H, HC=CH_2); 6.58 (d × d, 1H, HC=C); 6.7 (s, 1H, NH). $C_{11}H_{17}O_5N$ (243.25) Calcd.: C, 54.31; H, 7.05; N, 5.76. Found: C, 54.21; H, 6.86; N, 5.89.

(±)-2-*Amino*-3-*butenoic acid hydrochloride* **8**. A mixture of **7** (2.4 g, 10 mmol), 6N HCl (10 ml) and methanol was refluxed for 2 hours. After concentration under reduced pressure the residue was dried overnight over P_2O_5. The resulting solid was dissolved in hot methanol (10 ml) and diethyl ether (15 ml) was added. (±)-Vinylglycine hydrochloride crystallized upon cooling. Mp 178–183°c; (Lit.[19] 185–187°C), 0.85 g, 62%. ^{1}H-NMR (D_2O): 4.32 (d, 1H, HC-COOH); 5.50 (m, 2H, H_2C=); 6.04 (m, 1H, CH_2=CH). $C_4H_8NO_2Cl$ (137.72) Calcd.: C, 34.91; H, 5.81; N, 10.18. Found: C, 34.78; H, 6.08; N, 9.92.

New compounds: **3b**, **3c**, **3e**, **3f**, **4a**, **4b**, **5**, **6**.

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