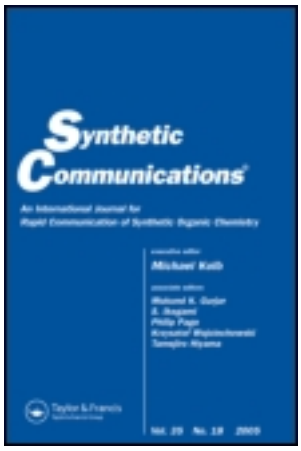

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CONJUGATE ADDITION OF THIOLS AND MALONATES TO THIOCINNAMATES UNDER PTC CONDITIONS

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ABSTRACT

Addition of thiols or diethylmalonate to thiocinnamate, under solid–liquid PTC conditions, afforded the corresponding 1,4-adducts in moderate to good yields. A 2-pyrrolidinone was obtained using diethyl *N*-acetamidomalonate as Michael donor, via intramolecular cyclization of the parent adduct.

Key Words: Thiocinnamates; Conjugate addition; Phase transfer catalysis; Pyrrolidinone

Conjugate addition to α,β-unsaturated aldehydes, ketones and carboxylic acid esters is one of the most valuable methods for carbon–carbon and carbon–heteroatom bond formation.[1] Stereochemical and mechanistic aspects of these classical reactions have been object of intense

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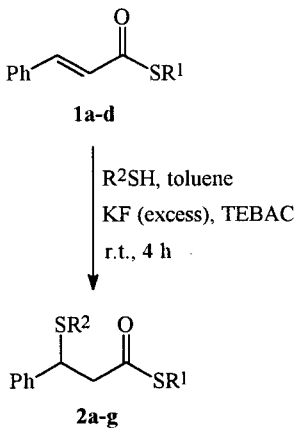
investigation, mainly focused on the direct addition of enolates or stabilized carbanions.[2]

In this communication we wish to report on the 1,4-addition of several thiols, diethylmalonate and diethyl *N*-acetamidomalonate to thiocinnamates, in a solid–liquid system, using TEBAC as phase transfer catalyst. It should be mentioned that α,β-unsaturated thiolesters were seldom used as acceptors in conjugate additions, and previously reported examples refer to reactions performed in homogeneous media.[3,4]

1,4-Addition of thiols to thiocinnamates: In our laboratory, the conjugate addition of a series of thiols to thiolesters **1a–d** was performed



1	R^1
a	Me
b	Ph
c	C_6H_4–Me (p)
d	C_6H_4–OMe (p)

2	R^1	R^2
a		Ph
b	Me	C_6H_4–Me (p)
c		C_6H_4–Cl (p)
d		C_6H_4–OMe (p)
e	Ph	Ph
f	C_6H_4–Me (p)	C_6H_4–Me (p)
g	C_6H_4–OMe (p)	C_6H_4–OMe (p)

Scheme 1.

using in situ generated benzyltriethylammonium fluoride[5] as catalytic phase transfer agent, and toluene as solvent (Scheme 1).

The reaction of thiocinnamate **1a** with four aromatic thiols afforded the expected 3-arylsulfanyl-3-phenyl-thiopropanoates in approximately the same yield (Table 1, Entries 1–4). As for compounds **1b–d**, good results could be obtained only if the R^1 and R^2 groups were the same (Table 1, Entries 5–7). If different thiols ($R^2 \neq R^1$) were allowed to react with thiocinnamates **1b–d**,

Table 1. Addition of Thiols to Thiocinnamates

Entry	PhCH=CHCOSR[1] **1**	R^1	R^2	PhCH(SR^2)CH_2COSR^1 **2** Yield[a] (%)
1	**1a**	Me	Ph	**2a** (76)
2	**1a**		C_6H_4-Me (p)	**2b** (73)
3	**1a**		C_6H_4-Cl (p)	**2c** (70)
4	**1a**		C_6H_4-OMe (p)	**2d** (68)
5	**1b**	Ph	Ph	**2e** (87)
6	**1c**	C_6H_4-Me (p)	C_6H_4-Me (p)	**2f** (82)
7	**1d**	C_6H_4-OMe (p)	C_6H_4-OMe (p)	**2g** (73)

Table 2. ^{13}C NMR Chemical Shifts[a] for Chalcone and **1a–d**

Compound	$\delta_{C\text{-}\alpha}$	$\delta_{C\text{-}\beta}$	$\delta_{C=O}$
PhCH = CHCOPh	122.0	144.4	189.9
1a	124.9	140.2	190.0
1b	124.4	141.8	188.1
1c	124.4	141.6	188.6
1d	124.3	141.5	189.1

[a]ppm/$CDCl_3$.

complex mixtures of mixed adducts were formed, probably due to the nucleofugality of the arylsulfanyl group at the thiolester moiety.

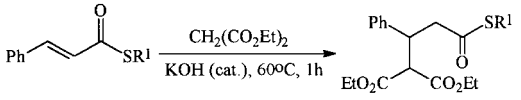
It is noteworthy that, in all cases, blank experiments, performed in the absence of catalyst, led to complete recovery of starting materials.

1,4-Addition of malonates to thiocinnamates: The conjugate addition of malonates to hindered Michael acceptors has been performed under PTC conditions, in the absence of solvent.[6] In particular, for additions to chalcone, this methodology proved to be superior to classical ones. In view of these findings, we became interested in investigating the reactivity of unsaturated thiolesters **1a–d** towards diethylmalonate and diethyl *N*-acetamidomalonate, under the same reaction conditions.

It should be mentioned that considering the similarity of ^{13}C NMR chemical shifts of carbonyl and double bond carbons for compounds **1a–d**, as compared to chalcone (Table 2), a similar trend of reactivity would be expected for the unsaturated ketone and thiolesters.

Results for the addition of diethylmalonate to acceptors **1a–d**, in the presence of catalytic amount to potassium hydroxide and in the absence of

Table 3. Michael Addition of Diethylmalonate to Thiolesters **1a–d**



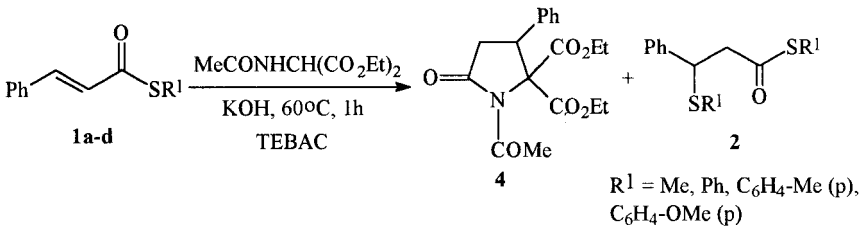
1 **3**

			Yield[a] (%)	
	R^1		TEBAC	No PTC Catalyst
1a	Me	**3a**	70	40
1b	Ph	**3b**	46	38
1c	C_6H_4-Me (p)	**3c**	44	37
1d	C_6H_4-OMe (p)	**3d**	60	43

[a]Isolated pure product after column chromatography on silica, using benzene as eluent.

solvent, are summarized in Table 3. As can be noted, the uncatalyzed interfacial process led to products in roughly the same yield, independently of the sulfur substituent at the thiolester group. However, some significant differences were observed under PTC conditions.

However, analogous reaction using diethyl *N*-acetamidomalonate instead of diethylmalonate, afforded a mixture of *N*-acetyl-4-phenyl-5,5-dicarbethoxy-2-pyrrolidinone **4** and β-sulfanylated thiolester **2** (Scheme 2).



Scheme 2.

The formation of the heterocyclic ring can be attributed to an intramolecular cyclization of the former Michael adduct. Competitive 1,4-addition of the liberated thiolate anion to the starting thiolester could be partially responsible for the low yield of compound **4** (Table 4).

Table 4. Michael Addition of Diethyl *N*-Acetamidomalonate to Thiolesters **1a–d**

Thiolester	**4** Yield[a] (%)	**2** Yield[a,b] (%)
1a	33 (4)[c]	[d]
1b	36 (8)[c]	14
1c	44 (12)[c]	16
1d	47 (6)[c]	8

[a]Column chromatography on silica using hexane/acetone (9:2).
[b]After recrystallization from hexane.
[c]In the absence of catalyst.
[d]Not isolated.

A better insight on the limitations of this new methodology for building the γ-lactam ring resulted from an experiment employing 100% molar excess of **1b**. For the same reaction time (1 h), no improvement in yield was observed. However, when the same reaction was performed adding an extra catalytic amount of TEBAC after 30 min, the yield of isolated pure pyrrolidinone **4** increased to 66%. A possible explanation for this result relies on the known ability of thiolate ions in promoting dealkylation of quaternary ammonium salts,[7,8] leading to catalyst deactivation.

In summary, we have demonstrated that α,β-unsaturated thiolesters react chemoselectively (1,4-addition) with thiols and malonates. Moreover, a new route to a functionalized pyrrolidinone could be improved by circumventing in situ catalyst decomposition.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer, using tetramethylsilane as internal standard. Melting points were determined using an Electrothermal model 9100 apparatus and are uncorrected. Microanalyses were performed on a Perkin Elmer 2400 B CHN elemental analyzer. Gravity column chromatography was performed on Merck Kieselgel 60 (70–230 mesh). Thiocinnamates **1a–d** were prepared according to literature procedures.[9]

Addition of thiols to thiocinnamates 1a–d. General procedure: Thiol (5.0 mmol) and thiocinnamate (6.3 mmol) were added, under N_2 atmosphere

Table 5. Physical, Spectroscopic, and CH-Analytical Data for **2a–g**

Compd.	M.p. (°C)	^{1}H NMR δ ($CDCl_3$), J (Hz)	Molecular Formula	Calcd.		Found	
				C	H	C	H
2**a**	81–82	2.24 (s, 3H); 3.18 (d, 2H, $J=7$), 4.74 (t, 1H, $J=7$); 7.22–7.34 (m, 10H)	$C_{16}H_{16}OS_2$	66.63	5.59	66.41	5.53
2b	115–118	2.21 (s, 3H); 2.29 (s, 3H); 3.14 (d, 2H, $J=7$); 4.65 (t, 1H, $J=7$); 7.03 (d, 2H, $J=8$); 7.17–7.25 (m, 7H)	$C_{17}H_{18}OS_2$	67.51	6.00	67.40	5.93
2c	92–95	2.24 (s, 3H); 3.14 (d, 2H, $J=7$); 4.68 (t, 1H, $J=7$); 7.10–7.32 (m, 9H)	$C_{16}H_{15}ClOS_2$	59.52	4.68	59.48	4.54
2d	111–114	2.22 (s, 3H); 3.14 (d, 2H, $J=7$); 3.76 (s, 3H); 4.56 (t, 1H, $J=7$); 6.72–6.78 (m, 2H); 7.13–7.25 (m, 7H)	$C_{17}H_{18}O_2S_2$	64.12	5.70	64.04	5.73
2e	73.5–76	3.24 (d, 2H, $J=7$); 4.73 (t, 1H, $J=7$); 7.20–7.55 (m, 15H)	$C_{21}H_{18}OS_2$	71.96	5.18	72.14	5.14
2f	95–97	2.30 (s, 3H); 2.33 (s, 3H); 3.21 (d, 2H, $J=7$); 4.65 (t, 1H, $J=7$); 7.02–7.31 (m, 13H)	$C_{23}H_{22}OS_2$	72.98	5.86	72.92	5.99
2g	80–82	3.19 (d, 2H, $J=7$); 3.74 (s, 3H); 3.76 (s, 3H); 4.56 (t, 1H, $J=7$); 6.73–7.70 (m, 13H)	$C_{23}H_{22}O_3S_2$	67.29	5.40	67.42	5.36

Table 6. Physical, Spectroscopic and CHN-Analytical Data for **3a–d/4**

Compd.	M.p. (°C) Eluent	^{1}H NMR δ ($CDCl_3$), J (Hz)	Molecular Formula	Calcd. C	Calcd. H	Found C	Found H
3a	52–54/A	0.98 (t, 3H, $J=7$); 1.25 (t, 3H, $J=7$); 2.16 (s, 3H); 3.05 (d, 2H, $J=7$); 3.71 (d, 1H, $J=10$); 3.87–4.00 (m, 3H); 4.19 (q, 2H, $J=7$); 7.18–7.25 (m, 5H)	$C_{17}H_{22}O_5S$	60.34	6.55	60.29	6.58
3b	47–48/A	1.00 (t, 3H, $J=7$); 1.27 (t, 3H, $J=7$); 3.13–3.17 (m, 2H); 3.78 (d, 1H, $J=10$); 3.89–4.00 (m, 3H); 4.22 (q, 2H, $J=7$); 7.18–7.36 (m, 10H)	$C_{22}H_{24}O_5S$	65.98	6.04	65.89	5.92
3c	79–80/A	0.98 (t, 3H, $J=7$); 1.25 (t, 3H, $J=7$); 2.31 (s, 3H); 3.03–3.23 (m, 2H); 3.78 (d, 1H, $J=10$); 3.88–4.06 (m, 3H); 4.21 (q, 2H, $J=7$); 7.05–7.29 (m, 9H)	$C_{23}H_{26}O_5S$	66.65	6.32	66.72	6.34
3d	61–63/A	0.97 (t, 3H, $J=7$); 1.24 (t, 3H, $J=7$); 3.09–3.14 (m, 2H); 3.74 (s, 3H); 3.76–3.98 (m, 4H); 4.20 (q, 2H, $J=7$); 6.82 (d, 2H, $J=2$); 6.86 (d, 2H, $J=2$); 7.08–7.28 (m, 5H)	$C_{23}H_{26}O_6S$	64.17	6.09	64.14	6.21
4	106–107/B	0.87 (t, 3H, $J=7$); 1.30 (t, 3H, $J=7$); 2.57 (s, 3H); 3.04 (d, 2H, $J=9$); 3.64–3.83 (m, 2H); 3.90 (t, 1H, $J=9$); 4.30 (q, 2H, $J=7$); 7.15–7.20 (m, 2H); 7.30–7.83 (m, 3H)	$C_{18}H_{21}NO_6$	62.25	6.09	62.23	6.16
				(N Calcd 4.03 Found 3.94)			

and magnetic stirring, to dry toluene (12.5 mL) containing TEBAC (0.02 mmol) and potassium fluoride (7.5 mmol). The resulting mixture was further stirred for 4 h, and then diluted with dichloromethane. The organic extract was treated with 10% aqueous sodium hydroxide and water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from hexane. (See Table 5).

Addition of malonates to thiocinnamates 1a–d. General procedure: A mixture of thiocinnamate (1.40 mmol), malonate (1.40 mmol), KOH (0.14 mmol) and TEBAC (0.14 mmol) was vigorously stirred at 60°C for 1 h. The reaction mixture was diluted with dichloromethane (30 mL), the organic extract was treated with aqueous HCl (10%) and water, and then dried over anhydrous magnesium sulfate. After removal of solvent under reduced pressure, the crude product was purified by column chromatography using (A) benzene or (B) hexane/acetone (9 : 2 v/v). (See Table 6).

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