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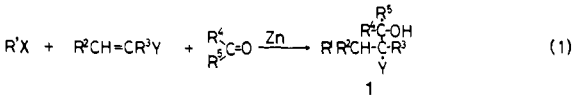
One-Step Joining Reaction of Thiolate Anions, Activated Olefins, and Carbonyl Compounds

Sir:

Conjugate addition of organometallic reagents to α,β-unsaturated compounds followed by trapping of the resulting anionic intermediates with nucleophiles has been accepted as a versatile tool in organic synthesis,[1] and we have previously reported a zinc-promoted one-step joining reaction of alkyl halides, activated olefins, and carbonyl compounds[1a] (eq 1).

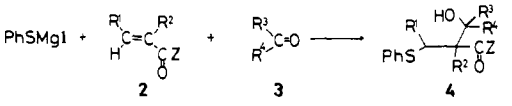


(1)

X = halogen
Y = electron-withdrawing group

Concerning these reactions, however, further chemical modification of the group R^1 starting from the products **1** is not necessarily possible.

In the present study, we have found a new one-step joining reaction (eq 2) in which metal thiolates[2] are used as the organometallic reagents, and hence the products **4** have a wide potential in organic synthesis since the thiolate group can easily be eliminated by a variety of methods.[3] The results are shown in Table I.



(2)

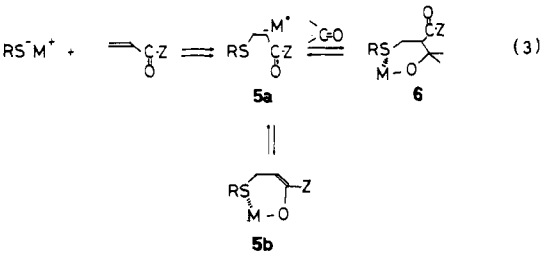
Z = alkyl or alkoxy group

Table I. One-Step Joining Reaction of Thiolate Anions, Activated Olefins, and Carbonyl Compounds

Activated Olefins (**2**)	Carbonyl Compounds R^3COR^4 (**3**)	Products[a,b] (**4**)	Isolated Yield (%)
2a, $R^1=R^2=H$, $Z=OMe$	**3a**, $R^3=i\text{-}Pr$, $R^4=H$	**4a**,	96
2a	**3b**, $R^3=Ph$, $R^4=H$	**4b**,	95
2a	**3c**, R^3 = 2-furyl, $R^4=H$	**4c**,	87
2a	**3d**, $R^3=R^4=-CH_3$	**4d**,	89
2a	**3e**, $R^3=R^4=-(CH_2)_5-$	**4e**,	72
2b, $R^1=H$, $R^2=CH_3$, $Z=OMe$	**3a**	**4f**,	97
2b	**3c**	**4g**,	92
2b	**3d**	**4h**,	95
2c, $R^1=CH_3$, $R^2=H$, $Z=OMe$	**3a**	**4i**,	90
2c	**3f**, $R^3=n\text{-}C_6H_{13}$, $R^4=H$	**4j**,	83
2c	**3d**	**4k**,	92
2d, $R^1=R^2=H$, $Z=CH_3$	**3a**	**4l**,	100
2e, 	**3a**	**4m**, 	90

[a] Spectroscopic and elemental analyses of all products were satisfactory for assigned structures. [b] A mixture of diastereomers.

In this joining reaction, the nature of solvent and the counterion (M^+) of the thiolate anion play important roles in the determination of the reaction pathway (eq 3).



(3)

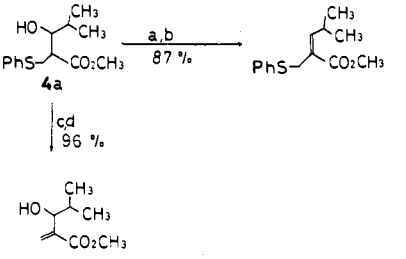
5a **6** **5b**

When M^+ is Li^+ or Na^+ and the reaction is carried out in polar solvents such as DMF or acetonitrile, the reaction stops with **5a,b.**[4] The use of MgI^+ as M^+ and nonpolar solvent such as ether and hexane is essential to achieve this joining reaction, since the intermediate **6** can become more stable under these conditions,[5] although the use of Na^+ as M^+ has been reported in a similar stepwise joining reaction in which the second step is the irreversible Wittig-Horner reaction.[6]

This new reaction is characterized by (1) mild reaction conditions, (2) high yields, (3) reasonably wide variety of the compounds **2** and **3**, and (4) high potentiality of the products **4** in organic synthesis as exemplified in Schemes I-III.[7] Scheme II shows a new synthetic route to α-methylene-γ-butyrolactones.[10]

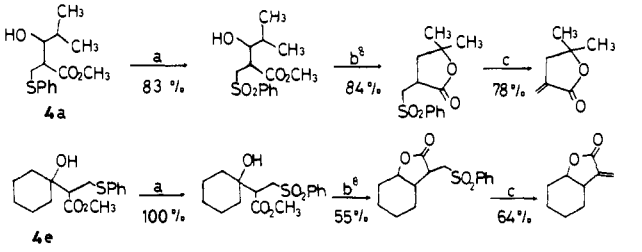
A typical experimental procedure is as follows. To a solution of phenylthiomagnesium iodide[12] (20 mmol) in hexane (20

Scheme I[a]



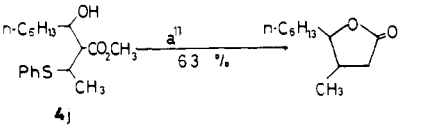
[a] (a) CH_3SO_2Cl, pyridine, room temperature. (b) reflux in pyridine; (c) $NaIO_4$, MeOH–H_2O–benzene (1:1:0.05); (d) reflux in toluene.

Scheme II[a]



[a] (a) *m*-Cl-PBA; (b) concentrated H_2SO_4, room temperature; (c) Na_2CO_3 in DMF, room temperature.

Scheme III[a]



[a] (a) Electroreduction.

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mL) and ether (20 mL) was added dropwise a solution of **2** (20 mmol) and **3** (20 mmol) in 20 mL of ether at 0 °C over a period of 2 min. After the reaction mixture was kept at room temperature for another 3 h, the usual workup[13] gave **4** in the isolated yields shown in Table I. Further extention of this new joining reaction in organic synthesis will be reported shortly.

References and Notes

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(7) All compounds in Schemes I–III showed reasonable results for assigned structures on spectroscopic and elemental analyses.
(8) This lactonization was carried out according to the method[9] of Dobrev, A.; Ivanov, C., et al.
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(11) The conditions of electroreduction were as follows: substrate (10 mmol); solvent, dry DMF (40 mL); cathode, Pb; anode, Pt; supporting electrolyte, tetraethylammonium *p*-toluenesulfonate (0.3 M); buffer, solid KH_2PO_4 (3 g); 0.3 A of direct current. The detail of this electroreductive skeletal rearrangement is not clear yet. In the absence of MgX^+, however, compounds of type **4** dissociate into carbonyl compounds and compounds of type **5a** under basic conditions. Thus, the formation of the γ-butyrolactone from **4j** seems to result from the electroreductive coupling of methyl β-phenylthiopropionate with *n*-heptanal since the cathodic solution became basic in the electroreduction. The scope and limitation of this novel electroreductive coupling will be reported elsewhere.
(12) Phenylthiomagnesium iodide was prepared by addition of a solution of thiophenol (20 mmol) in 20 mL of hexane to a solution of methylmagnesium iodide (20 mmol) in ether (20 mL).
(13) The reaction mixture was poured into large excess of an aqueous saturated solution of ammonium chloride, and the organic layer was extracted with ether. Products were isolated by column chromatography.

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Saturation-Transfer Study of the Mechanism of Proton Exchange in Amides

Sir:

The mechanism of proton exchange in amides has been a subject of interest for many years.[1] Two possibilities exist for acid-catalyzed exchange: (1) direct protonation on nitrogen (eq 1)[1a,b] and (2) protonation on oxygen, followed by proton abstraction from nitrogen to generate the imidic acid (eq 2).[1b,c]

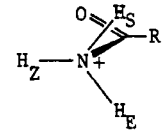
$$H^+ + RCONH_2 \rightleftharpoons RCONH_3^+ \qquad (1)$$

$$\Updownarrow$$

$$RC(OH)=NH_2^+ \rightleftharpoons RC(OH)=NH + H^+ \qquad (2)$$

We have previously concluded,[2] on the basis of indirect evidence, that such exchange in a variety of primary amides occurs via the N-protonation mechanism (eq 1), but with the additional feature that the lifetime of the intermediate, $RCONH_3^+$, is too short to permit rotational equilibration about the C–N single bond. We now present more compelling evidence, based on saturation-transfer experiments, that this mechanism is indeed involved, as well as evidence for the imidic acid mechanism (eq 2) in some cases. Redfield and Waelder[3] have independently obtained similar results for some different amides; their interpretation differs somewhat.

In primary amides, H_E and H_Z (protons respectively trans and cis to oxygen) are diastereotopic, and it is possible to measure each of their exchange rates separately. A distinction between these two mechanisms is provided by comparing rate constants for intermolecular and intramolecular exchange. Let k_{EZ} and k_{ES} be the pseudo-first-order rate constants for exchange from the E site to the Z site and to the solvent site, respectively; other k_{ij}'s are defined analogously. The imidic acid pathway requires that k_{EZ} and k_{ZE} be zero, since the configurational stability[4] of the imidic acids precludes acid-catalyzed intramolecular exchange. In contrast, protonation on nitrogen initially produces[2] the most stable conformer (**1**),



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with H_Z eclipsing oxygen. This conformer can lose H_S or H_E, but loss of H_Z requires rotation about the C–N single bond, whereupon H_Z exchanges with equal probability into the solvent and E sites. Therefore, the N-protonation mechanism requires that $k_{ZS} = k_{ZE}$. The distinction between the imidic acid and N-protonation routes thus depends on whether k_{ZE} is zero or equal to k_{ZS}, respectively. Moreover, in the N-protonation mechanism, to the extent that the lifetime of $RCONH_3^+$ is too short to permit rotational equilibration about the C–N bond, H_E will exchange faster than H_Z. It can be shown that k_{ES}/k_{ZS} or $k_{SE}/k_{SZ} = 1 + k_d/k_r$, where k_d and k_r are first-order rate constants for diffusion-controlled deprotonation[5] and rotation of $RCONH_3^+$, respectively.

Line-shape analysis is too inaccurate for comparing intramolecular exchange with intermolecular exchange. Therefore we have extended[6] the NMR saturation-transfer technique of Forsén and Hoffman[7] to the determination of all six rate constants of a three-site system. The method involves the measurement of not only intensities but also longitudinal relaxation times in Fourier-transform NMR spectra under conditions of selective saturation. These are the same measurements as in NOE (nuclear Overhauser enhancement)[8] studies, except that kinetic transfer of saturation leads to decreases in intensities. The experimental details of this technique are given elsewhere.[6]

We have applied this technique to the proton-exchange kinetics of four primary amides and one imidic ester. In the studies reported here, amides were examined in ethylene glycol, whose high solvent viscosity produces reasonably narrow line widths (8–9 Hz) for H_E and H_Z. Acid-catalyzed exchange was induced by addition of microliter quantities of 0.5 M HCl or concentrated sulfuric acid. Base-catalyzed exchange was induced with phosphate buffers. Nonexchanging samples (acetate buffered) were also examined for each amide. Apparent rate constants measured under nonexchange conditions were subtracted from rate constants measured for acidic or basic samples, to remove contributions from uncatalyzed rotation about the C–N partial double bond and from E–Z cross relaxation.[8] For comparison, water-catalyzed exchange in protonated ethyl acetimidate,[9] $CH_3C(OEt)NH_2^+Cl^-$, was studied in 32% v/v aqueous sulfuric acid. A nonexchanging sample, in 45% v/v aqueous sulfuric acid, served to correct for cross relaxation.

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