Pergamon

Tetrahedron 55 (1999) 193–200

TETRAHEDRON

Tetraethylammonium Hydrogen Carbonate in Organic Synthesis: Synthesis of Oxazolidine-2,4-diones.

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Received 24 July 1998; revised 12 October 1998; accepted 29 October 1998

Abstract: Oxazolidine-2,4-diones were synthesised by tetraethylammonium hydrogen carbonate (TEAHC) promoted carboxylation of secondary carboxamides bearing a leaving group at the α-position. Several oxazolidine-2,4-diones, including clinically used malidone®, have been prepared in moderate to excellent yields as a results of a formal proton extraction-carboxylation-intramolecular S_N2 one-pot sequence.

INTRODUCTION

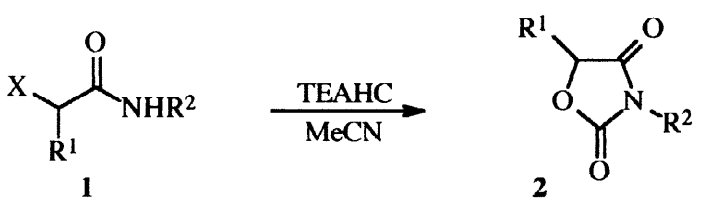
Recently, we found that tetraethylammonium carbonate (TEAC) and hydrogen carbonate (TEAHC), the first simply obtained by electrochemical reduction of carbon dioxide in aprotic polar solvent containing tetraethylammonium perchlorate (TEAP) as supporting electrolyte, and the second by reaction of tetraethylammonium hydroxide with carbon dioxide, showed carboxylating properties towards different classes of organic compounds. In particular, the reaction with amines[1] and alcohols[2] gave the corresponding organic carbamates and carbonates. When the substrates are not able to undergo carboxylation (*e.g.* thiols and pyrroles), TEAHC and TEAC show basic properties yielding, after the addition of a suitable alkylating reagent, the corresponding alkylation products.[3] According to the above-mentioned reactivity, we postulated that the reaction of TEAHC with amides bearing a leaving group at the α-position would constitute a method for the synthesis of oxazolidine-2,4-diones.

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01025-4

Oxazolidine-2,4-diones are biologically active compounds which find use as anticonvulsants.[4] Particularly interesting therapeutic properties were found in trimethadione® (3,5,5-trimethyloxazolidine-2,4-dione), paramethadione® (5-ethyl-3,5-dimethyloxazolidine-2,4-dione) and malidone® (3-allyl-5-methyloxazolidine-2,4-dione).[5] Recently, several compounds belonging to this class were shown to display a remarkable herbicidal activity and this discovery prompted the search for more efficient syntheses to replace the classical routes employing toxic and hazardous reagents such as phosgene or isocyanates.[4]

The most obvious and convenient approach to oxazolidine-2,4-diones can be considered to involve a formal incorporation of carbon dioxide into an amide followed by an intramolecular S_N2 reaction with a leaving group. Our research group, in the past, was involved in a study concerning the transformation of amides by way of electrochemical methodologies.[6] Oxazolidine-2,4-diones were obtained by (i) carboxylation of 2-haloacetamides *via* their electrodic reduction in the presence of CO_2,[7] (ii) the reaction of halo- and tosylamides with an electrogenerated base (EGB) and carbon dioxide,[8] (iii) the reaction of electrogenerated $O_2^{\cdot-}$ / CO_2 system with amides bearing a leaving group at the α-position.[9] All these methods replace toxic and harmful reagents with mild and safe electrogenerated reagents.

Herein, we report a simple and safe methodology for the synthesis of oxazolidine-2,4-diones (**2**) by reaction of secondary amides bearing a leaving group at the α-position (**1**) with TEAHC (eq. 1).



1 **2** (eq. 1)

X = Cl, Br, OTs

R^1 = H, Alkyl
R^2 = Alkyl, Aryl, Benzyl, Allyl

RESULTS AND DISCUSSION

Oxazolidine-2,4-diones were obtained, employing very mild reaction conditions and short reaction times, by reacting *N*-alkyl and *N*-aryl amides bearing a leaving group at the α-position with TEAHC in acetonitrile at room temperature. The results are reported in Table 1. Good yields of oxazolidine-2,4-diones where obtained when the substituent at the nitrogen atom was an alkyl or benzyl group (entries 1-3; 7-12), but were lower when a phenyl group was present (entries 4-6). These results are consistent with a reaction

pathway involving carboxylation followed by cyclization of the resulting carbamate ion (Scheme 1). The low yield of the cyclic compound obtained employing *N*-phenylamides **1d-f** can be attributed to the poor nucleophilicity of the anion, owing to the charge delocalization on the aromatic ring.

Table 1. Synthesis of Oxazolidine-2,4-diones (**2**) from *N*-Alkyl and *N*-Aryl Acetamides Bearing a Leaving Group at the α-Position (**1**).

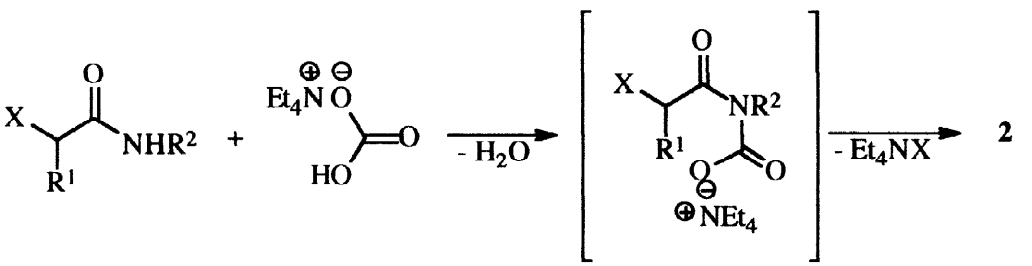
Entry	Substrate	R^1	R^2	X	Product	Yield (%)[a]
1	**1a**	H	CH_2Ph	Cl	**2a**	86
2	**1b**	H	CH_2Ph	Br	**2a**	85
3	**1c**	H	CH_2Ph	OTs	**2a**	87
4	**1d**	H	Ph	Cl	**2b**	45
5	**1e**	H	Ph	Br	**2b**	47
6	**1f**	H	Ph	OTs	**2b**	41
7	**1g**	CH_3	$(CH_2)_3Ph$	Br	**2c**	75
8	**1h**	CH_3	$(CH_2)_3Ph$	OTs	**2c**	96
9	**1i**	CH_3	$CH_2CH=CH_2$	Br	**2d**	93
10	**1j**	H	CH_3	Cl	**2e**	84
11	**1k**	CH_3	CH_3	Br	**2f**	82
12	**1l**	CH_2CH_3	CH_3	Br	**2g**	82
13	**1m**	H	Ts	Br	**1m**	98

[a] Yields refer to isolated product.

Concerning the leaving group effect, if this group lies on a primary carbon, the yield of the cycle was not influenced by the nature of the leaving group (entries 1-3). In addition, when the cyclization involves a secondary carbon, the yield of oxazolidine-2,4-dione seems to depend on the leaving group nature (entries 7-8). 2-Bromo-*N*-tosylpropionamide **1m** was found to be unreactive, probably because the tosyl group renders the amide unable to undergo the carboxylation reaction; **1m** was recovered nearly quantitatively after treatment of the reaction mixture with mineral acid. Malidone® **2d** was obtained in 93% yield from *N*-allyl-2-bromopropionamide **1i**.

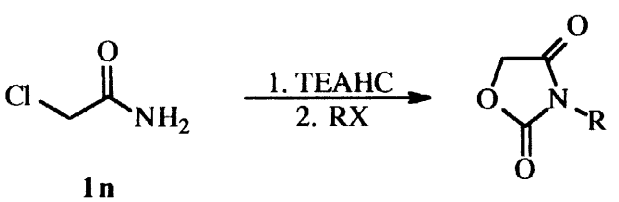
In attempts to obtain 3,5,5-trisubstituted oxazolidine-2,4-diones (trimethadione® and paramethadione®) both bromoamides **1k** and **1l** and oxazolidine-2,4-dione **2g** were allowed to react with TEAHC and methyl iodide. Even using a large excess of hydrogen carbonate and alkylating reagents, the

cyclic compounds **2f** and **2g** were recoreved showing that TEAHC is not basic enough to perform the subsequent deprotonation of the C_5-H bond of the oxazolidine-2,4-dione. In any case this reaction can be accomplished by using electrochemical methodologies as reported in a previous paper.[8]



Scheme 1. Plausible Reaction Pathway for the Reaction of Amides Bearing a Leaving Group at the α-Position with TEAHC.

Finally, in order to verify the generality of the method also for the synthesis of 3-unsubstituted derivatives, chloroacetamide **1n** has been submitted to the carboxylation-cyclization process, (Scheme 2) but the corresponding oxazolidine-2,4-dione **2h** was obtained (using a molar ratio amide/TEAHC 1:2) only in poor yield (29%) after extraction with organic solvents of the acidified reaction mixture. Alternatively, *in situ* alkylation of the initial reaction product can be performed. The corresponding 3-alkyloxazolidine-2,4-diones **2i** and **2a** were obtained in fair yield.



1n

RX = HCl	**2h** (29%)
RX = CH_3CH_2I	**2i** (46%)
RX = $PhCH_2Br$	**2a** (68%)

Scheme 2. Reaction of Amide **1n** with TEAHC followed by Hydrochloric Acid and by Alkylating Reagents.

Acknowledgment. This work was supported by research grants from M.U.R.S.T. Rome, Italy.

EXPERIMENTAL

General. Flash column chromatography was performed on ICN silica gel (230-400 mesh).[10] Melting points were taken upon a Tottoli apparatus and are uncorrected. IR spectra were recordered on a Perkin Elmer 281B grating spectrophotometer. ^{1}H (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded with a Bruker AC 200 spectrometer using $CDCl_3$ as internal standard (*s*: singlet, *t*: triplet, *q*: quartet, *qt*: quintet, *b*: broad, *m*: multiplet). GC-MS measurements (EI, 70 eV) were carried out on a Supelco SP2250 30m x 0.32mm capillary column using a Varian Saturn 2000 gas chromatography-mass detector system equipped with a ion trap mass selective detector. Dry acetonitrile (Lab-scan, anhydroscan) was used as received. TEAHC was prepared as reported by Venturello[11] starting from a methanol solution (25% w/w) of TEAOH (Fluka). The reagent was dried under vacuum for 24 hours and then was stored under argon.

Synthesis of amides. Chloroacetamide **1n** was purchased (Aldrich) and used as received. Chloroacetamides **1a, d** were obtained by reaction of chloroacetyl bromide (Aldrich, 10 mmol) with benzylamine and aniline (20 mmol), respectively, in CH_2Cl_2 solution (30 mL) at 0 °C for 2 hours. After washing with water (15 mL), saturated NH_4Cl (3 × 15 mL) and water (15 mL), the solution was dried ($MgCl_2$), and the solvent was removed under reduced pressure. Bromoacetamides **1b, e, g, i** were synthesised by reaction of bromoacetyl and 2-bromopropionyl bromide with the appropriate amine according to the above-mentioned procedure. Bromotosylamide **1m** was prepared from bromoacetylbromide and toluene-4-sulfonamide as already reported.[8] Flash chromatography and/or crystallization of the crude residue allowed the isolation of the amide.

N-Benzylchoroacetamide (**1a**),[12] *N*-benzylbromoacetamide (**1b**),[13] *N*-phenylchloroacetamide (**1d**),[7] *N*-phenylbromoacetamide (**1e**),[14] *N*-allyl-2-bromopropionamide (**1i**)[15] and *N*-tosyl-2-bromoacetamide (**1m**)[8] are known compounds; product assignment was determined by their ^{1}H-NMR spectra, ^{13}C-NMR spectra and elemental analysis compared to authentic materials or literature assignments.

***N*-(3-Phenylpropyl)-2-bromopropionamide 1g.** Flash chromatography (30% ethyl acetate in light petroleum) afforded **1g** (98 %) as a pale yellow solid. m.p. 60-61 °C. IR (nujol) ν: 3270, 3080, 1650 and 1560 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.32-7.12 (*m*, 5H, arom.); 6.59 (*bs*, 1H, N*H*); 4.37 (*q*, J = 7.0 Hz, 1H, C*H*Br); 3.25 (*q*, J = 7.0 Hz, 2H, NCH_2); 2.64 (*t*, J = 7.6 Hz, 2H, CH_2Ph); 1.96-1.75 (*m*, 5H, CH_3C, CCH_2C).

^{13}C NMR ($CDCl_3$) δ (ppm): 169.2, 141.1, 128.5, 128.4, 128.3, 128.2, 126.0, 45.0, 39.6, 33.0, 30.7, 22.9. GC-MS (EI, 70 eV) m/z: 271 (M^+ + 1, 32%), 270 (M^+ 8), 269 (20), 190 (14), 162 (46), 118 (23), 117 (39), 91 (52), 86 (100), 65 (17), 55 (19). Anal.Calcd. for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97, N, 5.18. Found: C, 53.11; H, 6.13; N, 4.99.

N-Methyl haloacetamides **1j-l** were obtained by reaction of methylamine (Aldrich, 40% wt. in water; 20 mmol) with the appropriate ethyl or methyl haloester (1:1.1 molar ratio) in ethanol or methanol (15 mL) at room temperature. The raction was monitored by TLC. Evaporation of the solvent and purification of the solid residue by flash chromatography and/or crystallization afforded the desired amide.
N-Methylchloroacetamide (**1j**),[16] *N*-methyl-2-bromopropionamide (**1k**)[15] and *N*-methyl-2-bromobutyramide (**1l**)[20] are known compounds; product assignment was determinated by their ^{1}H-NMR spectra, ^{13}C-NMR spectra and elemental analysis compared to authentic materials or literature assignments.

O-Tosylglycolamides **1c, f, h** were prepared by reacting the corresponding bromoamide with silver toluene-4-sulfonate.[8]
N-Benzyl-*O*-tosylglycolamide (**1c**)[17] and *N*-phenyl-*O*-tosylglycolamide (**1f**)[17] are known compounds; product assignment was determinated by their ^{1}H-NMR spectra, ^{13}C-NMR spectra and elemental analysis compared to authentic materials or literature assignments.

***N*-(3-Phenylpropyl)-*O*-tosyllactamide 1h.** Flash chromatography (50% ethyl acetate in light petroleum) afforded **1h** (50%) as a white solid. m.p. 61-62 °C. IR (nujol) ν: 3290, 1660, 1600 and 1540 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (*d*, J = 8.5 Hz, 2H, *arom.*); 7.36-7.11 (*m*, 7H, *arom.*); 6.30 (*bs*, 1H, N*H*); 4.81 (*q*, J = 6.9 Hz, 1H, C*H*CO); 3.29-3.15 (*m*, 2H, NCH_2); 2.62 (*t*, J = 7.0 Hz, 2H, CH_2Ph); 2.40 (*s*, 3H, CH_3C$_6$H$_4$); 1.76 (*qt*, J = 7.0 Hz, 2H, CCH_2C); 1.39 (*d*, 3H, J= 6.9 Hz, CH_3C). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.7, 145.6, 141.1, 133.0, 130.1, 128.5, 128.3, 127.9, 126.1, 38.9, 33.0, 30.9, 21.6, 18.7.). Anal.Calcd. for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41, N, 3.88. Found: C, 63.41; H, 6.24; N, 4.04.

Synthesis of oxazolidine-2,4-diones. General procedure. Amide **1** (1 mmol) was added, at room temperature, to a stirred solution of TEAHC (1.5 mmol) in acetonitrile (15 mL). The reaction was monitored by TLC. The solvent was then evaporated and the residue was washed with Et_2O (3 × 10 mL). The ethereal solution was evaporated under reduced pressure and the residue purified by flash chromatography (or crystallization) to give oxazolidine-2,4-diones **2**. When **1n** was used as starting compound a 1:2.2 amide-

TEAHC molar ratio was used and hydrochloric acid or alkyl halides were added after 2 hours to the reaction mixture.

3-Benzyloxazolidine-2,4-dione (**2a**),[8] 3-phenyloxazolidine-2,4-dione (**2b**),[18] 3-allyl-5-methyloxazolidine-2,4-dione (**2d**),[8, 18] 3-methyloxazolidine-2,4-dione (**2e**),[19] 3,5-dimethyloxazolidine-2,4-dione (**2f**),[19] 3-methyl-5-ethyloxazolidine-2,4-dione (**2g**),[21] oxazolidine-2,4-dione (**2h**)[22] and 3-ethyloxazolidine-2,4-dione (**2j**)[21] are known compounds; product assignment was determined by their ^{1}H-NMR spectra, ^{13}C-NMR spectra and elemental analysis compared to authentic materials or literature assignments.

3-(3-Phenylpropyl)-5-methyloxazolidine-2,4-dione 2c. Flash chromatography (35% ethyl acetate in light petroleum) afforded **2c** (75%) as a pale yellow oil. IR (nujol) ν: 1810 and 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.31-7.05 (*m*, 5H, *arom.*); 4.69 (*q*, J = 7.0 Hz, 1H, OC*H*CO); 3.56 (*t*, J = 7.1 Hz, 2H, NCH_2); 2.64 (*t*, J = 7.2 Hz, CH_2Ph); 1.99 (*qt*, J = 7.2 Hz, 2H, CCH_2C); 1.50 (*d*, J = 7.0 Hz, 3H, CH_3C). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.5, 140.4, 128.4, 128.2, 126.1, 75.8, 39.9, 32.8, 28.5, 16.5. MS (EI, 70 eV) m/z: 233 (M^+, 90%), 118 (68), 117 (100), 115 (16), 91 (69), 77 (23), 65 (24), 56 (19), 51 (16), 39 (16).). Anal.Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48, N, 6.00. Found: C, 66.76; H, 6.67; N, 5.82.

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