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A Synthetic Route to 5-Aryl-2-oxazolidinone Derivatives

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Synopsis. 5-Aryl-2-oxazolidinones have been synthesized readily by the elimination of dimethylamine from the corresponding (2-hydroxyethyl)ureas. The ureas are obtainable by the photoreaction of tetramethylurea with *para*-substituted benzaldehydes (Method A) or with *para*-substituted methyl benzoates (Method B). The electronic character of the substituent on the benzene ring determines which method is suitable for the preparation of (2-hydroxyethyl)ureas.

2-Oxazolidinones (*e.g.*, Furazolidone[1a] and Methoxadone[1b]) are of pharmaceutical importance,[2] and research has been devoted to establishing convenient synthetic routes for 2-oxazolidinones.[3—5] Most of the reported methods, however, consist of tedious multiple steps.[6]

As part of the studies on the application of *N*,*N*-dimethylcarbamoyl compounds to synthetic chemistry,[5,7—10] a convenient synthetic route to 5-aryl-2-oxazolidinones (**7**) by the photoreaction of tetramethylurea with aromatic compounds such as benzaldehyde and methyl benzoate, followed by the thermal cyclization has been found.

It may be reasonable to consider that the exploitation of convenient synthetic route to **3** is essential, because the desired ones (**7**) are accessible from a series of (2-hydroxyethyl)ureas (**3**) in satisfactory yields as described later. Consequently one-step preparation for **3**, through photochemical hydrogen abstraction of the *para*-substituted benzaldehydes (**1**) from tetramethylurea (**2**) was designed.

Irradiation of an acetonitrile solution of **1** and **2** gives the desired ureas (**3**) in one-step, although the yields are low as shown in Table 1, together with pinacols derived from the photoreduction of the corresponding **1** (20—40%) and dimeric urea (**4**). In some cases, **7** was also found, for example, **1c** gave **7c** (11% yield).

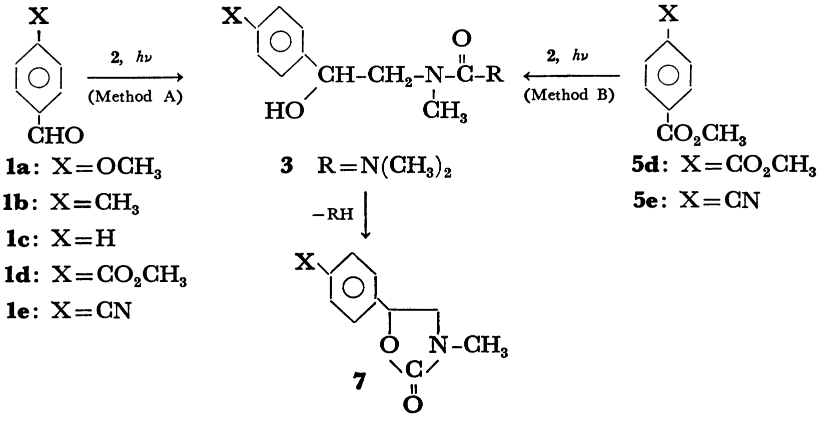
The ureidomethylation (Method A) is apparently induced by hydrogen abstraction by the excited n-π* triplet state of **1** from **2**. The formation of **3** was heavily suppressed in the case of **1d** and **1e** which has an electron withdrawing group substituent in the benzene ring because of the low efficiency for hydrogen abstraction.[11]

To overcome this defect in Method A, the photoreaction of *para*-substituted methyl benzoates (**5**) with **2** (Method B) was designed, based on the result that the photoreaction of aromatic esters such as **5d** or **5e** in an appropriate hydrogen donating solvent readily affords some alcohol derivatives derived from reduction

TABLE 1. YIELDS AND SPECTRAL DATA OF 3

Compound[a]	Yield/%[b]	IR ν/cm^{-1}	NMR(in $CDCl_3$) δ/ppm
3a	29 (0.4)[c]	1600 820	2.8 (s, 6H), 2.83 (s, 3H), 3.0, 3.6 (ABX octet, 2H), 3.8(s, 3H), 4.9(ABX q, 1H), 5.9 (br s, 1H)[d], 6.3—7.4 (A_2B_2, 4H)
3b	28	1600 830	2.3 (s, 3H), 2.8(s, 9H), 3.0, 3.6 (ABX octet, 2H), 4.9 (ABX q, 1H), 5.8(br s, 1H), 7.0—7.4 (m, 4H)
3c	26 (11)[c]	e)	e)
3d	5 (2)[c] 53[f]	1715 1600 820	2.8 (s, 9H), 3.1, 3.6 (ABX octet, 2H), 3.9 (s, 3H), 5.0 (ABX q, 1H), 6.4 (d, 1H)[d], 7.0—8.0 (A_2B_2, 4H)
3e	7 11[f]	2200 1600 825	2.8 (s, 6H), 3.1 (s, 3H), 3.2 (ABX octet, 2H), 5.0 (ABX q, 1H), 6.0 (br s, 1H), 7.2—7.6 (m, 4H)

a) Satisfactory elemental analyses were obtained for all new compounds (**3**). b) Based on the consumed aldehydes (**1**) or esters (**5**), c) Yield of 2-oxazolidinones (**7**). d) D_2O exchangeable. e) Ref. 7. f) Method B.



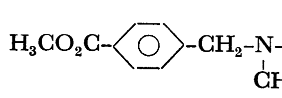
Scheme 1.

TABLE 2. YIELDS AND SPECTRAL DATA OF **7**

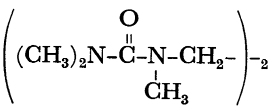
Compound[a)]	Yield/%[b)]	IR ν/cm^{-1}	NMR (in $CDCl_3$) δ/ppm
7a	69	1740	2.9 (s, 3H), 3.4, 3.8 (ABX sextet, 2H), 3.8 (s, 3H), 5.4 (ABX t, 1H), 6.8—7.4 (m, 4H)
7b	72	1730 825	2.3 (s, 3H), 2.9 (s, 3H), 3.4, 3.9 (ABX sextet, 2H), 5.4 (ABX t, 1H), 7.2—7.4 (m, 4H)
7c	79	1730 750 690	2.9 (s, 3H), 3.4, 3.9 (ABX sextet, 2H), 5.4 (ABX t, 1H), 7.2—7.4 (m, 5H)
7d	73	1730 1715 820	2.9 (s, 3H), 3.4, 3.9 (ABX sextet, 2H), 3.8 (s, 3H), 5.5 (ABX t, 1H), 7.3—8.0 (A_2B_2, 4H)
7e	77	2200 1740	2.9 (s, 3H), 3.4, 4.0 (ABX sextet, 2H), 5.5 (ABX t, 1H), 7.4—7.8 (A_2B_2, 4H)

a) Satisfactory elemental analyses were obtained for all new compounds (**7**). b) Based on the consumed ureas (**3**).

of the ester group and subsequent coupling of the resulting radicals.[12] Irradiation of **5d** with **2** in acetonitrile through a quartz filter led to the formation of **3d** in 53% yield. In the case of **5e**, photoureidomethylation of the aromatic ring described previously in aromatic nitriles[8] proceeded to give benzylurea (**6e**) (15% yield), and **3e** (11% yield).



6e



$$\left((CH_3)_2N\text{-}\overset{\overset{O}{\|}}{C}\text{-}\underset{CH_3}{N}\text{-}CH_2\text{-}\right)_2$$

4

(2-Hydroxyethyl)ureas (**3**), prepared by Method A or B, were subsequently subjected to thermal reaction. A solution of **3** (0.05 M) in xylene was refluxed for 10 h, enabling the cyclization to proceed smoothly to give the 5-aryl-2-oxazolidinone derivatives (**7**) in good yields (Table 2).

Experimental

Materials. Methyl terephthalaldehydate (**1d**) was obtained by the Sommelet reaction.[12] *p*-Cyanobenzaldehyde (**1e**) was prepared according to the procedure of Lieberman *et al.*[13] Methyl *p*-cyanobenzoate (**5e**) was prepared by the esterification of the corresponding acid. All other aldehydes, dimethyl terephthalate (**5d**) and tetramethylurea (**2**) were commercially available.

*General Procedure for Preparation of (2-Hydroxyethyl)ureas (**3**). Method A*: The aldehydes (**1**) and a three molar excess of tetramethylurea (**2**) were dissolved in acetonitrile. After nitrogen was bubbled through the solution for 15 min, the solution was irradiated with a 500 W high pressure mercury arc through a Pyrex filter for 10 h at room temperature. After evaporation of the solvent, the unreacted **2** was recovered *in vacuo* and the residue chromatographed on silica gel. The products (**3**) were eluted with a mixture of benzene–ether.

Method B: A solution of **5d** or **5e** and a ten molar excess of **2** in the same solvent was similarly irradiated through a quartz filter for 20 h. After irradiation, a similar procedure was conducted. From the volatile components, methanol was detected by GLC (20% PEG, 20 M on Celite 545). Benzylurea (**6e**) was confirmed by a comparison with an authentic sample alternatively prepared.

*Alternate Synthesis of 1-(*p*-Methoxycarbonylbenzyl)-1,3,3-trimethylurea (**6e**).* **6e** was prepared from *p*-methoxycarbonylbenzyl bromide and an excess of trimethylurea in the presence of potassium amide in liquid ammonia according to the method by Bryant *et al.*[14] Bp 120 °C (0.6 Torr); IR (neat) 1700, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.5 (s, 3H), 2.6 (s, 6H), 3.8 (s, 3H), 4.4 (s, 2H), 7.2—8.0 (A_2B_2, 4H). Found: C, 62.22; H, 7.39; N, 10.90%. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19%.

*General Procedure for Synthesis of 5-Aryl-2-oxazolidinones (**7**).* A solution of **3** (0.35—0.45 mmol) in xylene (8 ml) was heated under reflux for 10 h. After removal of the solvent, the residue was chromatographed on silica gel. Elution with benzene–ether gave **7**.

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