Tetrahedron Letters,Vol.29,No.40,pp 5095-5098,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ANOMALOUS RING OPENING OF N-ARYL-2-OXAZOLIDINONES BY ANHYDROUS ALKOXIDE: A CONVENIENT PREPARATION OF N-(ALKOXYETHYL)-2,6-DISUBSTITUTED ANILINES

L. W. Fancher* and R. D. Gless, Jr.**

Stauffer Chemical Company
de Guigne Technical Center
Richmond, CA 94804

R. Y. Wong

Bio-Rad Laboratories
Richmond, CA 94801

Abstract: N-(2-Alkoxyethyl)anilines may be prepared by acylation of an N-unsubstituted aniline with 2-chloroethyl chloroformate, ring closure to oxazolidinone, ring opening with alkoxide under anhydrous conditions to a carbamic acid salt, and decarboxylation. This unexpected mode of ring opening is especially useful in the preparation of N-(2-alkoxyethyl)-2,6-disubstituted anilines.

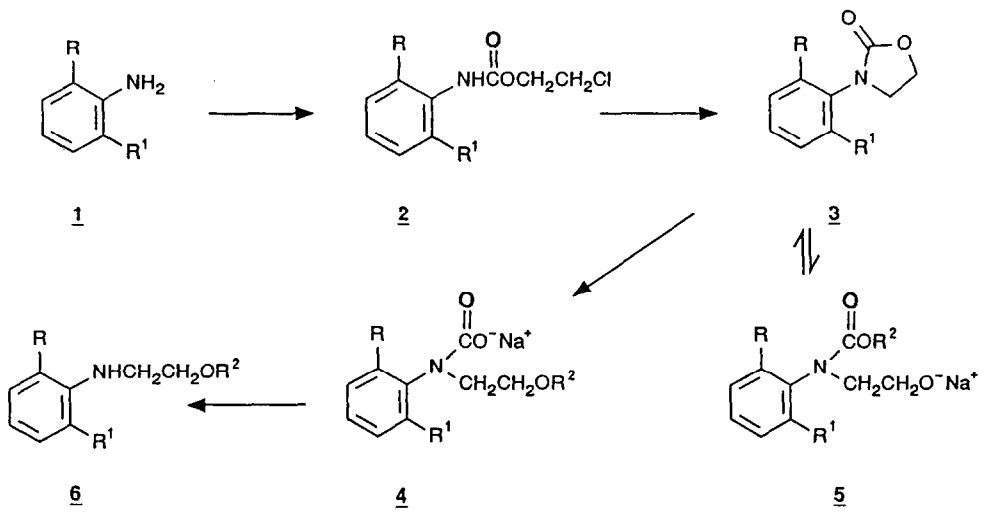
N-(2-Alkoxyethyl)-2,6-disubstituted anilines are important intermediates to analogs of commercial chloroacetanilide herbicides.[1,6] As such, synthesis of these materials has elicited considerable interest. Various methods of preparation have been reported, including alkylation of the desired aniline with epichlorohydrin and etherification,[2] condensation of the desired aniline with an alkoxyacetaldehyde and reduction,[3] amination of dialkylcyclohex-2-ene-1-ones and dehydrogenation,[4] alkylation of the desired aniline with methoxyethanol[5] or with an alkyl or arylsulfonate derivative of an alkoxy-ethanol,[6] and reduction of the corresponding alkoxyacetanilide.[7] All of these procedures suffer from some drawback, be it inconvenience for laboratory or large scale preparations, or the possibility for byproduct formation. We wish to report a simple preparation of these materials <u>via</u> an unexpected mode of ring opening of N-aryl-2-oxazolidinones by alkoxide. This approach affords a convenient preparation of multiple 2-alkoxyethyl derivatives from a single readily accessible oxazolidinone precursor which is ideal for large scale laboratory preparation of intermediates.

Mechanistic studies on the hydrolysis of N-phenyl-2-oxazolidinone **3k** report nucleophilic attack of hydroxide to proceed at the carbonyl group to form the corresponding N-(2-hydroxyethyl)carbamic acid **5k** (R^2 = H).[8] Treatment of N-(2,6-dimethylphenyl)-2-oxazolidinone **3a** with anhydrous methanolic sodium methoxide, however, afforded not the expected

*Retired **Author to whom correspondence should be addressed

N-(2-hydroxyethyl)carbamate **5a** (R^2 = CH_3), but the corresponding N-(2-methoxyethyl)carbamic acid **4a** (Scheme). This outcome is postulated to arise from the reversible nature of the ring opening under anhydrous conditions allowing reaction analogous to $B_{al}2$ ester cleavage to become the dominant reaction pathway. ^1H NMR and ^{13}C NMR experiments with **3j** in methanolic sodium methoxide showed no measurable buildup of N-(hydroxyethyl)carbamate **5j** (R^2 = CH_3) or a tetrahedral intermediate during the course of the reaction. The least hindered case, **3h**, required slightly longer reaction times in dilute alkoxide solution presumably due to stabilization from π overlap between the aryl group and the carbamate moiety in the oxazolidinone ring. Molecular models show the oxazolidinone ring is forced out of the plane of the aryl ring in the more substituted cases with increasing bulk of the ortho substituents on the aryl ring leading to increasing steric hindrance to attack at C-5 of the oxazolidinone ring.

SCHEME



N-(2-Alkoxyethyl)-2,6-disubstituted anilines are prepared in the following manner. Aniline **1** is acylated with 2-chloroethyl chloroformate[9] under Schotten-Baumann conditions with aqueous sodium hydroxide or with an amine base under anhydrous conditions. Treatment of the resulting carbanilide **2** with aqueous sodium hydroxide or aqueous methanolic sodium methoxide affords the corresponding oxazolidinone **3**.[10] Ring opening is effected with the alkoxide of choice followed by addition of acid to decarboxylate intermediate carbamic acid **4**. For larger scale preparations carbanilide **2** is conveniently converted to oxazolidinone **3** by treatment with one equivalent of alkoxide, followed by addition of more alkoxide and heating. When ring opening is complete, slow addition of aqueous hydrochloric acid to the hot reaction

mixture allows controlled decomposition of intermediate carbamic acid salt **4**. Overall yields of N-(2-alkoxyethyl)aniline **6** from 3 ranged from 67% - 96% (Table). Under typical reaction conditions (*e.g.*, 10% methanolic sodium methoxide at reflux), ring opening can require extended heating (50-80 hours). Reaction times can be reduced substantially on a small scale by superheating the reaction mixture, and, on a larger scale, by using higher concentrations of alkoxide (25% or greater) or pressures slightly above atmospheric. Ammonium chloride was used in place of hydrochloric acid during decarboxylation of the N-(2-*t*-butoxyethyl) analogs to prevent cleavage of the *t*-butyl ether.

Preparation of N-(2-Alkoxyethyl) Anilines

Compound	R	R^1	R^2	Yield[a]
6a	CH_3	CH_3	CH_3	96
6b	CH_3	CH_3	CH_2CH_3	92
6c	CH_2CH_3	CH_2CH_3	CH_3	89
6d	CH_3	CH_3	*i*-C_3H_7	90
6e	CH_3	CH_3	*n*-C_3H_7	89
6f	CH_3	CH_3	*t*-C_4H_9	87
6g	CH_2CH_3	CH_3	CH_3	67
6h	CH_2CH_3	CH_3	CH_2CH_3	91
6i	Cl	Cl	CH_3	82
6j	H	CH_3	CH_3	90
6k	H	H	CH_3	89

a) Overall yield from oxazolidinone **3** to product **6**. No attempt was made to optimize reaction yield.

Experimental

N-(2-Chloroethoxycarbonyl)-2,6-dimethylaniline **2a**: A 3 neck, 3 L round bottom flask fitted with a mechanical stirrer, dropping funnel, and thermometer was charged with 123 mL (121 g, 1.0 mole) 2,6-dimethylanilline, 500 mL toluene, and 440 mL 10% aq. NaOH (1.1 mole). 2-Chloroethyl chloroformate (108 mL, 150 g, 1.05 mole) was added dropwise to the vigorously stirred reaction mixture over 40 min maintaining an internal temperature of 25°C. At the end of the addition, the pH of the aqueous layer was 8. After stirring an additional 15 min, the pH of the aqueous layer (now 5-6) was adjusted to 11 with 30 mL of 10% aq. NaOH, and the mixture was stirred an additional 15 min. Glpc analysis[11] of the organic layer showed 0.4% **1a** and 98% **2a**. After phase separation, the toluene layer was stirred over Na_2SO_4 and evaporated to dryness at 50°C/25 mm Hg to afford 184 g (96.5%) of a light pinkish solid, mp 80-81.5°C (toluene). During larger scale preparations it was advantageous to heat the reaction mixture to 35°C before phase separation to prevent crystallization of **2a** during workup.

N-(2,6-Dimethylphenyl)-2-oxazolidinone **3a**: A one liter, 3 neck round bottom flask fitted with a thermometer, mechanical stirrer, N_2 sweep, and dropping funnel was charged with 78.1 g (0.344 mole) **2a** and 200 mL of CH_3OH. The resulting steel gray solution was treated with 82.5 mL of 25% methanolic $NaOCH_3$ over 5 min maintaining an internal temperature less than 30°C. After 3 h at room temperature, glpc analysis[11] showed 0.2% **2a** and 97% **3a**. After 5 h the reaction mixture was

poured into 1.2 L of water and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to afford 62.8 g (95.7%) of **3a** as a gray solid, mp 136.5-137°C (toluene).

N-(2-Methoxyethyl)-2,6-dimethylaniline **6a**: A 100 mL, 3 neck round bottom flask fitted with a thermometer, N_2 sweep, and reflux condenser was charged with 3.55 g (18.5 mmole) **3a** and 21.6 mL (94.4 mmole) of 25% methanolic $NaOCH_3$. The resulting mixture was heated in a 95°C bath to give an internal reaction temperature of 83°C. After 6 h, glpc analysis[11] of a worked-up aliquot of the reaction mixture showed no starting material remaining. The reaction was worked up by cautious addition of 30 mL of 6 M HCl to the hot reaction mixture over 3 min to afford gas evolution and formation of a white precipitate. After addition of acid was complete, the reaction mixture was heated at reflux for 30 min and cooled to room temperature. H_2O (20 mL) was added, and the mixture was extracted with 20 mL of toluene which was discarded. The aqueous layer was made basic by addition of 6 mL of 50% NaOH, and the separated oil was extracted with CH_2Cl_2 (3 x 25 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and evaporated to afford 3.16 g (95.5%) of a yellow oil which glpc analysis[11] showed to be 99% pure; bp 63-64.5°C/0.2 mm Hg, bp(lit.)[3] 64- 65°C/0.2 mm Hg.

References

1. Wegler, R., Chemie der Pflanzenschutz- und Schadlingsbekampfungsmittel, Vol. 5, Springer Verlag, 1977; Vol. 8, 1982.

2. Jap. Pat. Appl. 82/84852, May 16, 1984 to Kanesho Co. Ltd., Nippon Zeon Co. Ltd.; Chem. Abstr., 101, 19137k (1984).

3. Vogel, C. and Aebi, R., U. S. Pat. 4,283,221, Aug. 11, 1981 to Ciba Geigy, Corp.; Chem. Abstr., 95, 163902w (1981).

4. Brit. Pat. 1565849, Apr. 23, 1980 to Ciba-Geigy A.-G.; Chem. Abstr., 94, 30328w (1981).

5. Radlmerski, P. and Rusek, M., Eur. Pat. Appl. EP 4958, Oct. 31, 1979 to Ciba Geigy A.-G.; Chem. Abstr., 92, 128554a (1980).

6. Buehmann, U., Puttner, R. and Arndt, F., Ger. Pat. 1,802,662, Jul. 26, 1978, to Schering A.-G.; Chem. Abstr., 91, 157471f (1979); Vogel, C. and Aebi, R., Ger. Pat. 2,405,479, Aug. 14, 1974 to Ciba Geigy A.-G.; Chem. Abstr., 81, 151817v (1974).

7. Wong, R. Y., unpublished result.

8. Branstad, J. O., Acta Pharm. Suec., 6, 49 (1969); Chem. Abstr., 70, 114325k (1969).

9. Laboratory quantities of 2-chloroethyl chloroformate are available from Aldrich Chemical Company. Alternatively, this material may be prepared from epichlorohydrin (Naiki, K., J. Soc. Org. Syn. Chem. (Japan), 14, 84 (1956); Chem. Abstr., 57, 7018d (1962)) or ethylene oxide (Frevel, L. K. and Kressley, L. J., U. S. Pat. 2,820,809, Jan. 21, 1958 to Dow Chemical Co.).

10. Adams, R. and Segur, J. B., J. Am. Chem. Soc., 45, 785 (1923).

11. Gas chromatographic analyses were carried out under the following conditions: 10' x 1/4" 3% OV-17, stainless steel column, 100°C for 3 min then 10°C/min to 200°C for 3 min.

(Received in USA 23 June 1988)