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Trapping of Alkoxide Ions by Carbon Disulfide to Prevent Side Reactions in a Claisen Condensation. Synthesis of Methyl 2-(Aminomethylene)phenylacetamidoacetate

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Methyl 2-(aminomethylene)phenylacetamidoacetate was prepared by a Claisen condensation in the presence of carbon disulfide. Carbon disulfide traps liberated alkoxide ions as xanthate. Formation of methyl 2-(aminomethylene)formamidoacetate caused by alcoholysis of an intermediate is strongly decreased in the presence of carbon disulfide.

Polar aprotic solvents are superior as the reaction medium for this Claisen condensation.

Isocyanides react with 2-(Δ-3-thiazoline)acetic acids to form compounds with the fused β-lactam-thiazolidine ring system of penicillins as shown by Ugi.[1–3] Methyl 2-(aminomethylene)phenylacetamidoacetate (*4*) is the desired starting material for a 2-(Δ-3-thiazoline)acetic acid with the side chain of Penicillin G present in the α-position. Compounds containing the 2-(hydroxymethylene)formamidoacetate (*13*) moiety are referred to as penaldates.[4] They are prepared by Claisen condensations [5–7] or from oxazolones [8] and are converted into the corresponding aminomethylene compounds by treatment with ammonia. For the preparation of *4*, the oxazolone route was rejected, as no attractive synthesis of the oxazolone (*5*) was found. The corresponding 2-phenyl-5-oxazolone is easily prepared, but fails to react with methanol to the phenyl analog of *4* and with α-mercaptoisobutyraldehyde to a Δ-3-thiazoline.

This paper reports a modified condensation of methyl phenylacetamidoacetate (*1*) with methyl formate on the presence of carbon disulfide to give methyl 2-(aminomethylene)phenylacetamidoacetate (*4*). Previously described methods for preparation of *4* or the intermediary hydroxymethylene compound *3* give impure products in low yields.[2,6,7] In runs, where carbon disulfide is omitted methyl 2-(aminomethylene)formamidoacetate (*6*) is obtained as a by-product in a yield of 20 %.

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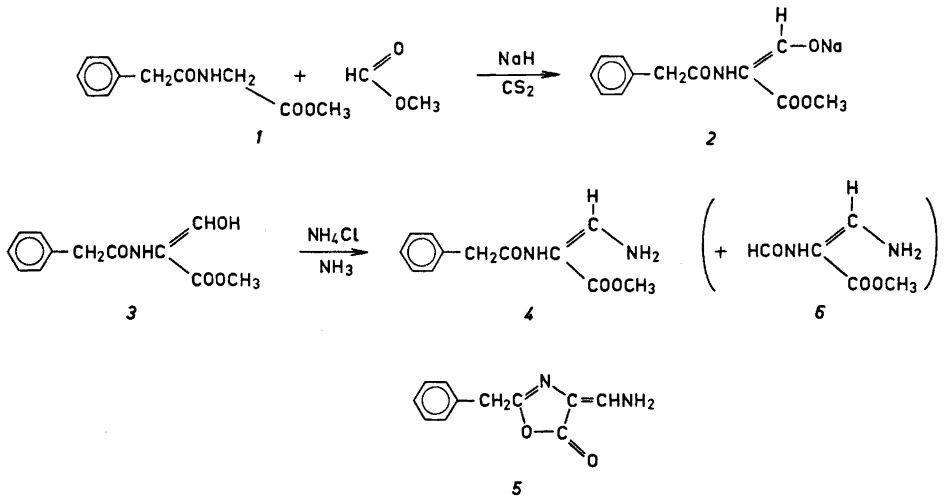

Fig. 1.

The reaction between methyl phenylacetamidoacetate (*1*) and methyl formate is quite complex. Self condensation of *1* cannot be avoided by using a large excess of methyl formate. Furthermore, alkoxide ions formed during the reaction cleave the amide bond giving fragments, which react further; *cf.* Fig. 2. This alcoholysis gives as much as 25 % of methyl phenylacetate (*7*) as reported earlier.[9] Methyl glycinate (*8*) and methyl 2-(aminomethylene)-glycinate (*14*) expected as the other fragments after alcoholysis of *1* and *2*, respectively, were not found in the reaction mixture. However, methyl 2-(aminomethylene)formamidoacetate (*6*) was isolated, indicating that the presence of methyl formate gives an *N*-formylation of the glycinate (*8*) or the 2-(hydroxymethylene)glycinate moiety (*12*); see Fig. 2.

By sublimation in a gradient tube *4* and *6* are conveniently separated in quantities of about 1 g. As separation of larger quantities by column chromatography could not be satisfactorily made, ways to decrease the formation of *6* were examined. To lower the concentration of methoxide ions, thus decreasing the undesired alcoholysis, the condensation was carried out in the presence of carbon disulfide and dimethyl sulfate, respectively. Carbon disulfide should trap methoxide ions as methyl xanthate and dimethyl sulfate should give dimethyl ether. As the presence of dimethyl sulfate led to a complex mixture, it was not further tried. Carbon disulfide greatly reduces the formation of methyl 2-(aminomethylene)formamidoacetate (*6*). According to Foye [10] carbon disulfide reacts with carbanions, but in this case no reaction products could be isolated from the starting material and carbon disulfide.

Self condensation of *3* is known to occur readily.[11] It was found advantageous to treat the crude sodium salt *2* with ammonium chloride in liquid ammonia, thus converting *3* directly upon liberation into the stable aminomethylene compound *4*.

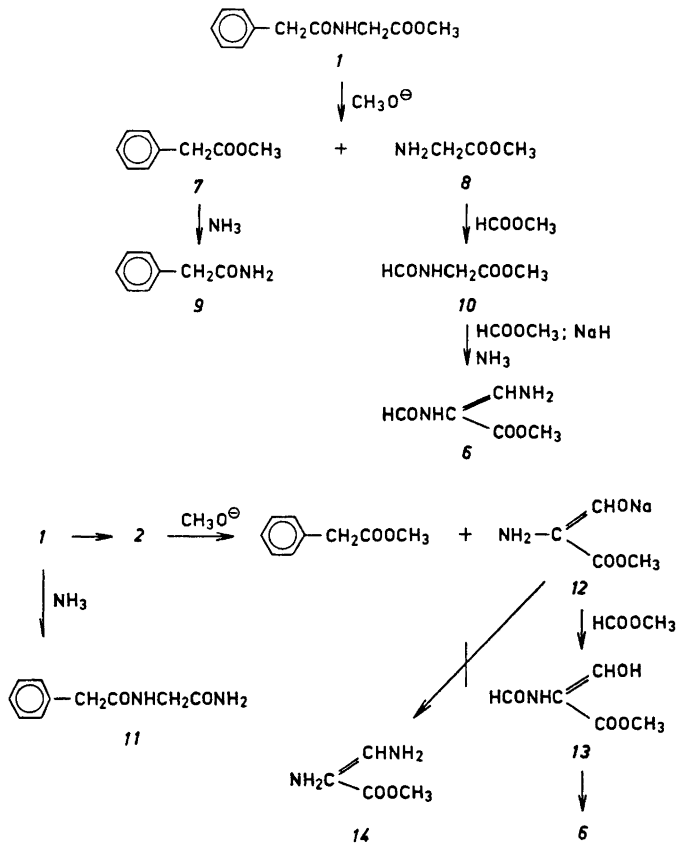

Fig. 2.

It is important that the sodium salt *2* is formed as a powdery precipitate in the medium chosen. Neutral compounds such as *1* and *7* can then be removed by washing. Thus contaminants such as phenylacetamide (*9*) and phenylacetamidoacetamide (*11*) formed using previous methods could be avoided.

The condensation was tried in different solvents. The best yields were obtained when using polar aprotic solvents[12] and not non-polar solvents, such as anhydrous benzene or ether as generally described.[6,7,13,14]

Actually, methyl formate alone or mixed with, *e.g.*, acetonitrile, provides an excellent medium. The following media, listed after decreasing yield of *4* were found efficient, *viz.* acetonitrile, diethylene glycol dimethyl ether, tetrahydrofuran, tetraethylene glycol dimethyl ether, dimethylformamide, hexamethylphosphoramide, monoethylene glycol dimethyl ether, and toluene. It should be noted that acetonitrile does not take part in the condensation. Benzene and diethyl ether as well as the polar tetramethylene sulfone proved to be less efficient solvents. No reaction occurred in ethylene carbonate.

Dimethyl sulfoxide cannot be used as a solvent as its anion, methylsulfinyl methanide, formed during the reaction, gives the corresponding β-sulfinyl ketones [15] with esters.

Sodium hydride [13,14] turned out to be the base giving the most satisfactory reaction. Two equivalents of base will direct the equilibrium of the condensation towards the enolate ion *2*. Less than two equivalents gives a lower yield and more of the starting material was recovered. Hauser and Walker recommend diethylamino magnesium bromide as a base in some mixed ester condensations.[16] In this case it was found less efficient. Sodium carbonate was also tried, but without success.

The best way to start the reaction is to charge the esters without a solvent. Acetonitrile containing carbon disulfide is then added dropwise to precipitate *3*. The appearance of the yellow color of sodium xanthate is an indication that the condensation has started. A combination of ultrasonical [17] and mechanical stirring gives a fine suspension of sodium hydride and prevents the lumping and foaming often met with, in Claisen condensations, which permits completion of the reaction within 15 min at 25°.

The NMR spectra of the aminomethylene compounds *4* and *6* indicate the presence of an NH bonded to the carbonyl group in the *cis*-form. Dudek [18,19] and Dabrovsky [20] have studied the *cis-trans*-isomerism of β-amino-α,β-unsaturated ketones and esters, showing that the two NH's appearing at different chemical shifts is valid for the *cis*-form, whereas in the *trans*-form they appear at the same shift. The *trans*-isomer of 4-amino-3-buten-2-one shows the two NH's at δ 4.8 and ethyl β-aminocrotonate shows one peak at δ 5.0 and one at δ 7.8.

The compounds *4* and *6* are now for the first time isolated in a crystalline form. The improvements of the reaction are mainly the addition of carbon disulfide to trap alkoxide ions, the use of a polar aprotic solvent, and the immediate conversion of *2* to *4*.

The idea of adding carbon disulfide as an agent for trapping of alkoxide ions has only been tried in this specific case. It might also be useful in other reactions where it is desirable to protect groups against attack by alkoxide ions as for instance to avoid transesterifications.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are not corrected. The IR spectra were recorded on a Perkin Elmer 237 Infrared Spectrometer, NMR spectra were recorded at 60 Mc/s on a Varian A 60 spectrometer and the UV spectra on a Beckman DK 2 instrument. Elemental analyses were carried out by Centrala Analyslaboratoriet, Kemikum, Uppsala.

Methyl 2-(aminomethylene)phenylacetamidoacetate (4). To a dried 500 ml Erlenmeyer flask, equipped with a Teflon stirrer and ultrasonic stirring, were charged 26.0 g (0.13 mol) of methyl phenylacetamidoacetate (*1*), 23.5 g (0.39 mol) of dry methyl formate,* and

* Previous to use the methyl formate was washed with a saturated sodium bicarbonate solution, dried over sodium sulfate and distilled twice over phosphorous pentoxide. Methyl phenylacetamidoacetate (1) was recrystallized from methanol : water 1 : 1, m.p. 85–87°. Acetonitrile was distilled over sodium hydride. Although the reaction was mostly run under an inert atmosphere it was found more important to use pure reagents, than thoroughly excluding humid air from the reaction vessel. Special care was taken to obtain dry methyl formate (*cf.* above).

13.0 g (0.27 mol) of 50 % sodium hydride in mineral oil. Then 9.9 g (0.13 mol) of carbon disulfide in 10 ml of dry acetonitrile were added dropwise with efficient stirring followed by 50 ml of dry acetonitrile, all within 10 min. Care was taken not to allow the temperature of the mixture to exceed 25°. After about 15 min when no more gas was evolved, 50 ml of dry diethyl ether were added. The precipitate was filtered off on a Büchner funnel, washed with 100 ml of dry diethyl ether and added portionwise to a solution of 15 g (0.28 mol) of ammonium chloride in 125 ml of liquid ammonia. After addition of 50 ml of acetonitrile, the ammonia was allowed to evaporate. The residue was extracted three times with 50 ml of refluxing acetonitrile. After removal of solvent, the crude product was washed with 20 ml of carbon tetrachloride giving a solid residue. The absence of impurities was checked by thin layer chromatography (Al_2O_3) using 1,2-dichloroethane : methanol, 10 : 1. Recrystallization from acetonitrile or sublimation in a gradient tube gave methyl 2-(aminomethylene)phenylacetamidoacetate (*4*). Yield 9.2 g (0.039 mol, 30 %); m.p. 170–172°; UV λ_{max} (C_2H_5OH) 266 nm ($\varepsilon = 18\,100$); IR (KBr) 3300 cm^{-1} (s), 3180 (s), 1650 (s), 1615 (m), 1490 (m), 1435 (m), 1370 (w), 1295 (s), 1185 (m), 1140 (m), 740 (w), 720 (m) and 680 (m). NMR (DMSO-d_6) $-COOCH_3$ $\delta = 3.55$ (s) 3H; $C_6H_5-CH_2-$ $\delta = 3.58$ (s) 2H; C_6H_5- $\delta = 7.33$ (s) 5H; four singlets each integrating 1H are present at $\delta = 6.07$, 6.25, 7.20, and 8.58. (Found: C 61.5; H 6.14. Calc. for $C_{12}H_{14}N_2O_3$ (234.3): C 61.5; H 6.02.)

Methyl 2-(aminomethylene)formamidoacetate (6). If the preceding reaction is run in the absence of carbon disulfide, two compounds can be isolated after sublimation of the crude product in the gradient tube. The less volatile compound is *4*; the most volatile compound was identified as methyl 2-(aminomethylene)formamidoacetate (*6*). By this method *4* and *6* were isolated in a ratio of 4 : 1. The following data were obtained for *6*. M.p. 155–157°. UV λ_{max} (C_2H_5OH) 266 nm ($\varepsilon = 19\,800$); IR (KBr) 3420 cm^{-1} (m), 3260 (s), 1675 (s), 1640 (s), 1520 (w), 1440 (m), 1390 (m), 1350 (m), 1300 (s), 1200 (m), 1125 (m), 995 (w), 870 (w), 800 (w), and 760 (w). NMR (CF_3COOH) $-COOCH_3$ $\delta = 3.95$ (s) 3H; six peaks each integrating 1H at $\delta = 5.86$, 6.75, 7.61, 7.81, 8.35 and 8.72. (Found: C 41.8; H 5.6. Calc. for $C_5H_8N_2O_3$ (144.1): C 41.7; H 5.6.)

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