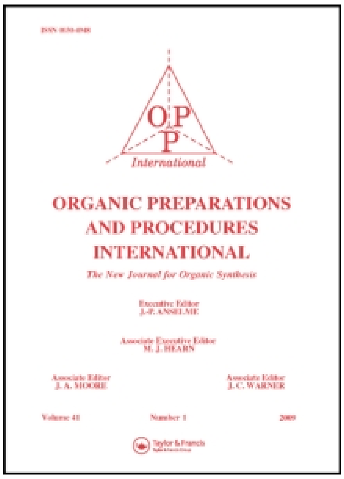

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A CONVENIENT SYNTHESIS OF ETHYL α-CARBETHOXY-β-(ARYLAMINO) ACRYLATES AND RELATED COMPOUNDS[†]

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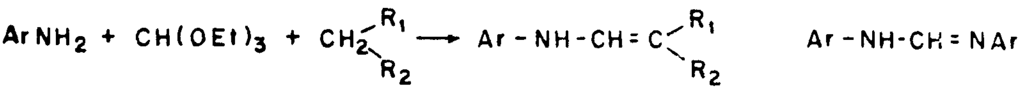
A variety of methods have been reported for the preparation of ethyl α-carbethoxy-β-(arylamino)acrylates,[1-3] which are valuable intermediates for the synthesis of biologically important quinoline derivatives. The conventional method involves the reaction of an arylamine with diethyl ethoxymethylene malonate in the presence of acetic acid[4] or of acetic anhydride and zinc chloride.[5] One of the main reactants of these methods, diethyl ethoxymethylene malonate is prepared separately from triethyl orthoformate and diethyl malonate in about 60% yield. A recent Hungarian patent describes the preparation of ethyl α-carbethoxy-β-(3-chloroanilino) acrylate by the reaction of a preformed bis(3-chloroanilino)formamidine with triethyl orthoformate, diethyl malonate and zinc chloride (or magnesium chloride hydroxide); however, the amount of zinc chloride was not specified.[6] A synthesis of ethyl α-carbethoxy-β-(m-chloroanilino) acrylate using m-chloroaniline, triethyl orthoformate and diethyl malonate with no catalyst is however, sluggish, requiring about 70 hrs for completion.[7]

We now report that ethyl α-carbethoxy-β-(arylamino) acrylates IV can be produced in less than 24 hrs in high yield and purity in a one-pot operation by using zinc chloride as catalyst. Thus a mixture of arylamine I was heated with half the



I II III IV V

stoichiometric quantity of triethyl orthoformate II at 130-135° for 2 hrs; the intermediate bis(aryl)formamidines V, without isolation, was treated with the remaining half of the stoichiometric quantity of II and diethyl malonate III in the presence of catalytic amounts of anhydrous zinc chloride at the same temperature for 5 hrs; this was followed by further addition of the remaining III and stirring for 15 hrs under identical conditions. The reaction was found to be very general in nature. Other methylene compounds such as ethyl acetoacetoacetate, ethyl cyanoacetate, malonitrile and acetylacetone can also be used in place of diethyl malonate(III). The reaction was very facile in the case of malononitrile and was complete within a total period of 8 hrs. The reaction failed with methyl phenylacetate and with methyl ethyl ketone. Our results are summarized in the Table. With 2-naphthylamine,ethyl α-carbethoxy-β-(2-naphthylamino)acrylate, mp. 78°, lit.[8] mp. 78°, was obtained in 88% yield. The pmr spectra of all the products showed a characteristic methine proton at δ 8.3-8.5 as a doublet (J = 13 Hz).

EXPERIMENTAL

Ethyl α-carbethoxy-β-anilinoacrylate(IV). General Procedure.- Aniline (37.2 g, 0.4 mole) and triethyl orthoformate (29.6 g, TABLE. Ethyl α-Carbethoxy-β-(arylamino)acrylates and Related Derivatives(IV)[a]

Cmpd.	R	R_1	R_2	Yield (%)	mp. (°C)	lit. mp. (°C)
IVa	H	CO_2Et	CO_2Et	94	50	50[10]
IVb	2-Cl	CO_2Et	CO_2Et	96	90	91[9]
IVc	3-Cl	CO_2Et	CO_2Et	94	56	57[10]
IVd	4-Cl	CO_2Et	CO_2Et	90	81	82[10]
IVe	4-OMe	CO_2Et	CO_2Et	86	oil	38[11]
IVf	3-Me	CO_2Et	CO_2Et	88	41	41[9]
IVg	$4-NO_2$	CO_2Et	CO_2Et	96	142	142[10]
IVh	2,4-diCl	CO_2Et	CO_2Et	86	112	112[12]
IVi	2-Cl	CO_2Et	CN	92	170[b]	-
IVj	3-Cl	CO_2Et	CN	96	126	126[2]
IVk	3-Cl	CN	CN	96	198	198[14]
IVl	3-Cl	CO_2Et	COMe	85	87	88[2]
IVm	4-OMe	CO_2Et	COMe	88	88	88[13]
IVn	3-Cl	COMe	COMe	80	92	92[2]

a. The pmr and IR spectra of the products and their elemental analyses were in accordance with their sturctures.

b. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17; Cl, 14.14

Found: C, 57.78; H, 4.51; N, 10.9; Cl, 14.00

0.2 mole) were stirred at 135° for 2 hrs and ethanol was distilled as it was being generated. To the resulting bis-(anilino)formamidine which was not isolated, were added in the same flask triethyl orthoformate (32.6 g, 0.22 mole), diethyl malonate (32 g, 0.2 mole) and freshly fused anhydrous zinc chloride (0.25 g) at 135° for 5 hrs. After that time, an additional 32 g (0.2 mole) of III was added and stirring was continued for 15 hrs at 135°. The reaction mixture was poured into 10% aqueous hydrochloric acid (50 ml). The product was extracted with chloroform. Removal of the solvent by distillation gave 99 g (94%) of ethyl α-carbethoxy-β-anilinoacrylate (IVa), mp. 50°, lit.[10] mp. 50°. The product is of sufficient purity for further reactions. The product can be recrystallized from petroleum ether, mp. 50°; pmr (CCl_4). δ 1.17-1.52 (3H, t, $-CO_2CH_2C\underline{H}_3$), 4.0-4.5 (2H, q, $-CO_2C\underline{H}_2CH_3$), 6.93-7.5 (m, Ar-H), 9.4 (d, J = 13 Hz; -CH=), 11.0 (d, -NH). In the cases of higher melting products, the products were separated from the aqueous hydrochloric acid by filtration and were of sufficient purity for use in further reactions.

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