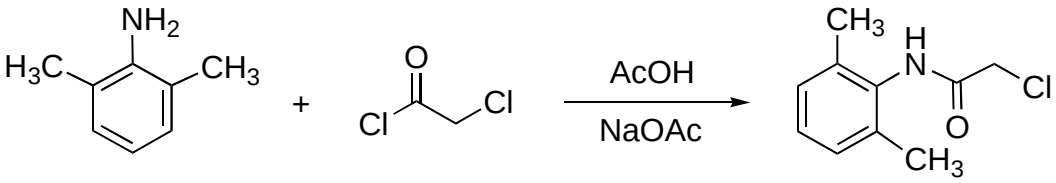
EXPERIMENTATION IN ORGANIC CHEMISTRY

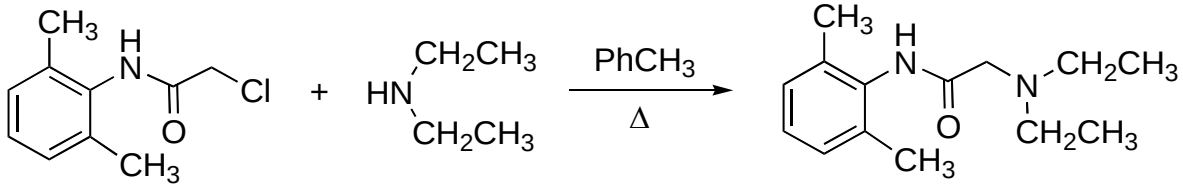
LESSON 6. FORMATION OF AMIDES AND NUCLEOPHILIC SUBSTITUTION REACTION (S_N2). SYNTHESIS OF LIDOCAINE

REACTIONS:

First step: Amidation



Second step: Nucleophilic Substitution Reaction (S_N2)



REAGENTS:

2,6-Dimethylaniline; glacial acetic acid; chloroacetyl chloride; sodium acetate (5% aqueous solution); toluene; diethylamine; 3N HCl; 6N potassium KOH; anhydrous Na_2SO_4; pentanes.

MATERIALS:

250 mL Erlenmeyer flask; pipette; heater equipped with magnetic stirring; Kitasato; Büchner funnel; 50 mL round bottomed flask; watch glass; reflux condenser; separation funnel.

PROCEDURE:

Amidation reaction: 2,6-Dimethylaniline (2.5 mL) is placed into a 250 mL Erlenmeyer flask. Glacial acetic acid (1 mL) is added and the mixture is shaken until it becomes homogeneous. Then, chloroacetyl chloride (1.8 mL) is carefully added through an addition funnel, maintaining a vigorous stirring (**CAUTION !!**, the reagent is tear-producing and gives off an intense odor, it must be carried out in the HOOD). After the addition, the mixture is heated to 45 ºC during aprox 5 minutes. Sodium acetate is added (50 mL, 5% aqueous solution) while stirring vigorously: a precipitate is formed during the process. The suspension is cooled down to ca. 10 ºC placing the flask in an ice-water bath for a while, and vacuum-filtered through a Büchner-Kitasato system. The solid is washed four times with cold water (40 mL each) to eliminate the rests of acetic acid. When the solid is dry enough, it is placed on a watch glass (previously weighted) and let completely drying overnight. The yield and the melting point of the product are determined.

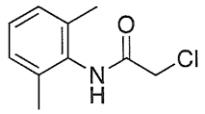
Substitution reaction: To a suspension of 1g of α-chloro-2,6-dimethylacetanilide in 10 mL of toluene (placed into a 50 mL round bottomed flask equipped with a stir bar) is added 1.5 mL of dimethylamine (with a pipette), the condenser is attached, and the mixture is heated under reflux for ca. 1 hour. Then, it is let cooling down to room temperature. In case some crystals appear during the process, discard them by filtering off under vacuum with a Büchner-Kitasato system and washed them with 10 mL toluene (take into account that Lidocaine will remain dissolved in the filtrate). The toluene used for washing is added to the filtrate.

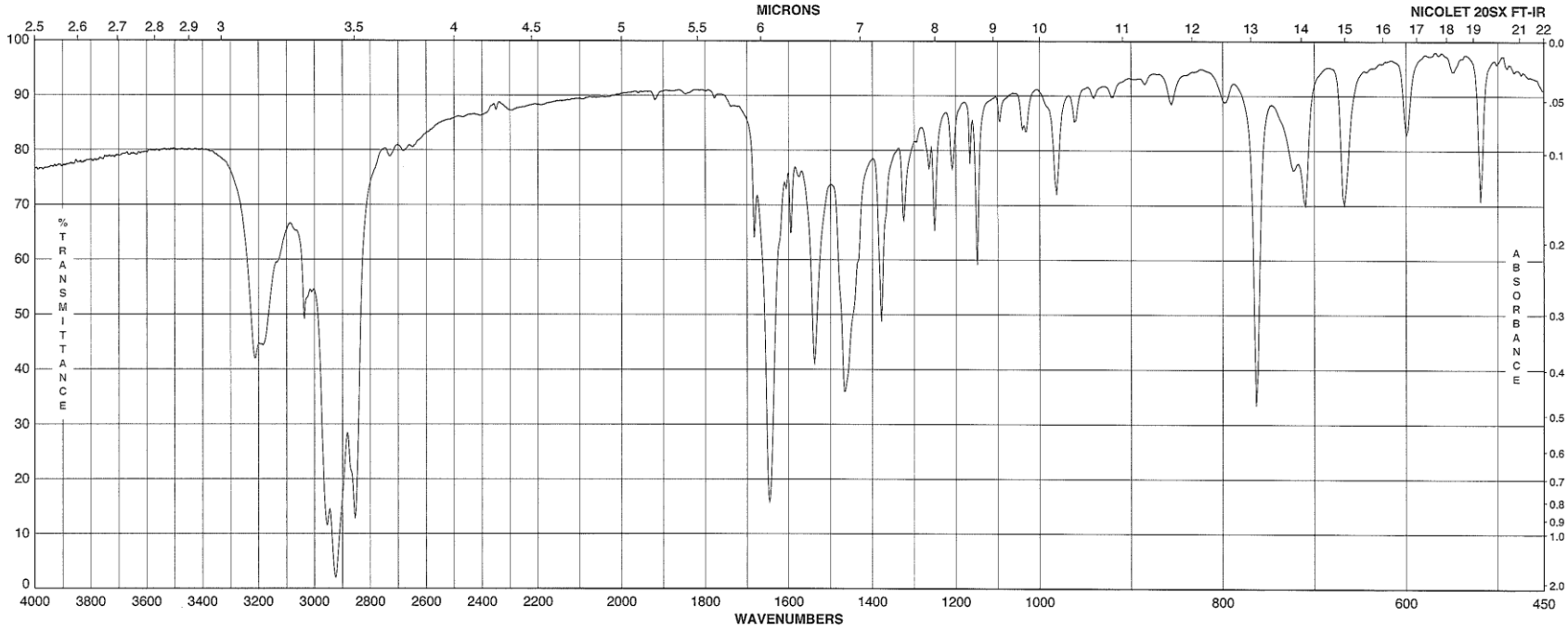
The fíltrate is placed in a separation funnel, 20 mL of 3N HCl are added, the mixture is shaken, and the lower aqueous phase is collected in a 250 mL Erlenmeyer flask. The organic phase is washed again with 20 mL HCl, and the resulting aqueous phase is added to the Erlenmeyer flask together with the previous one. Finally, the remaining organic phase is kept separately in another flask.

The Erlenmeyer containing the aqueous acid liquors is cooled down in an ice/water bath, keeping the temperature below 10 ºC. A 6 M solution of KOH is slowly dropped with a pipette until a Lidocaine precipitate is formed. (CAUTION, the reaction is exothermic, keep the temperature under control). A bit more of KOH is added, to assure complete precipitation of the product,

and the mixture is let warming up to room temperature.

Then, the mixture is placed into a separation funnel and 20 mL of pentanes are added, slightly shaking the funnel. The aqueous phase is eliminated, and the organic phase is washed with 15 mL of water, and shaken. Once again, the aqueous layer is eliminated and the operation is repeated a total of five times, before the organic phase is finally placed into a dry Erlenmeyer flask to be dried over Na_2SO_4. The liquid is filtered through a conical funnel (with filter paper) to eliminate the rests of Na_2SO_4, and the solvent is eliminated in the rotavap. The Lidocaine solid is weighted, the yield and the melting point are determined.


O
N
H
Cl


MICRONS
NICOLET 20SX FT-IR
2.5 2.6 2.7 2.8 2.9 3 3.5 4 4.5 5 5.5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 21 22
100 90 80 70 60 50 40 30 20 10 0
%TRANSMITTANCE
0.0 .05 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 2.0
ABSORBANCE
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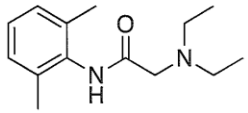
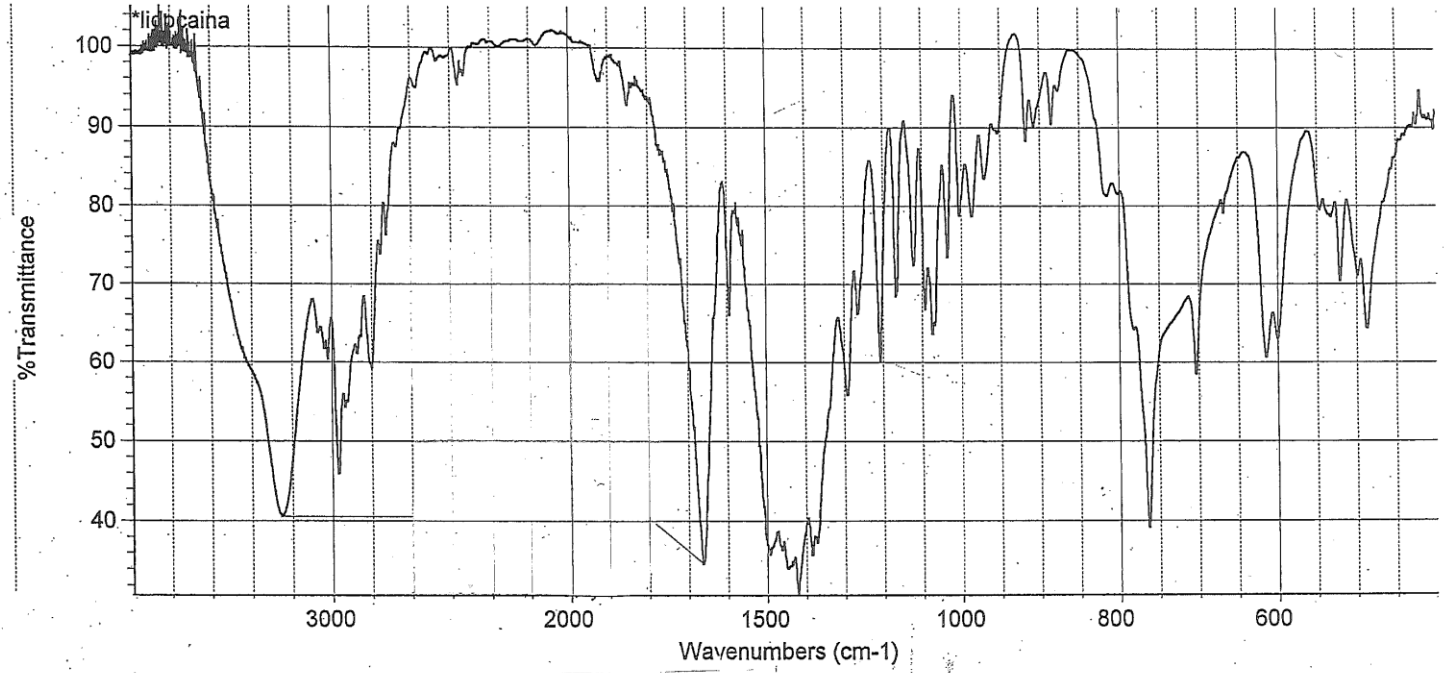
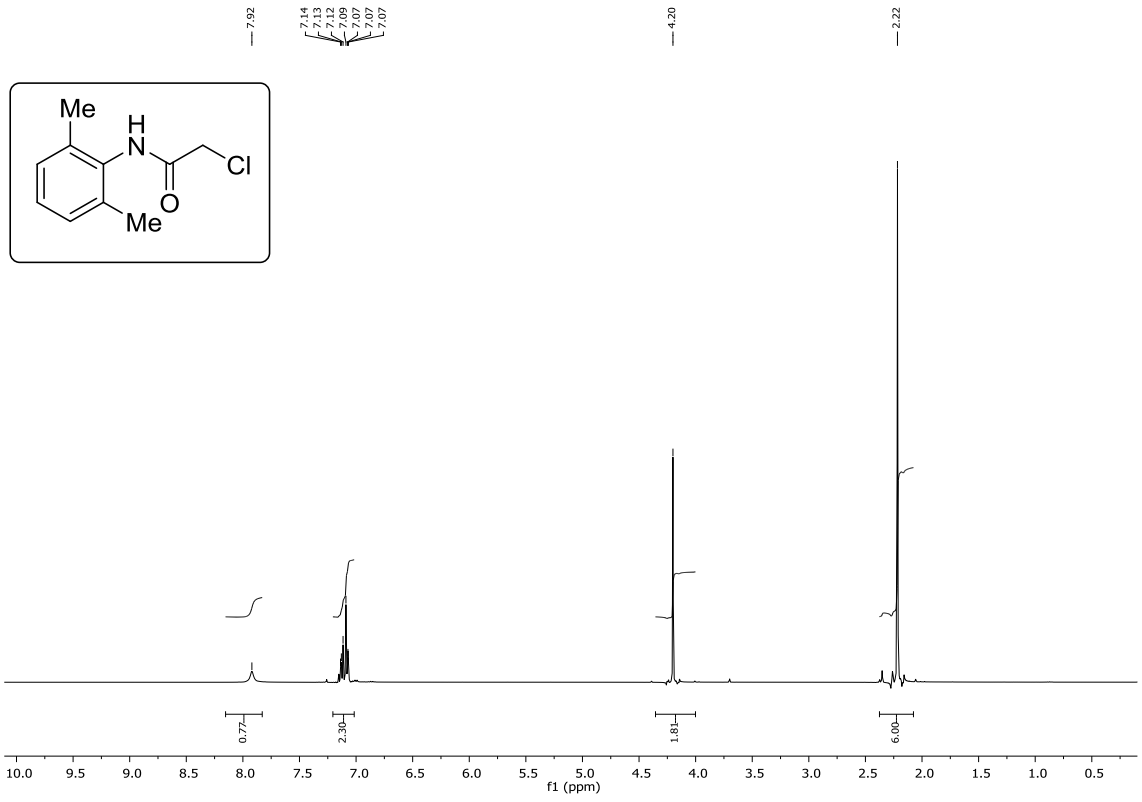
WAVENUMBERS



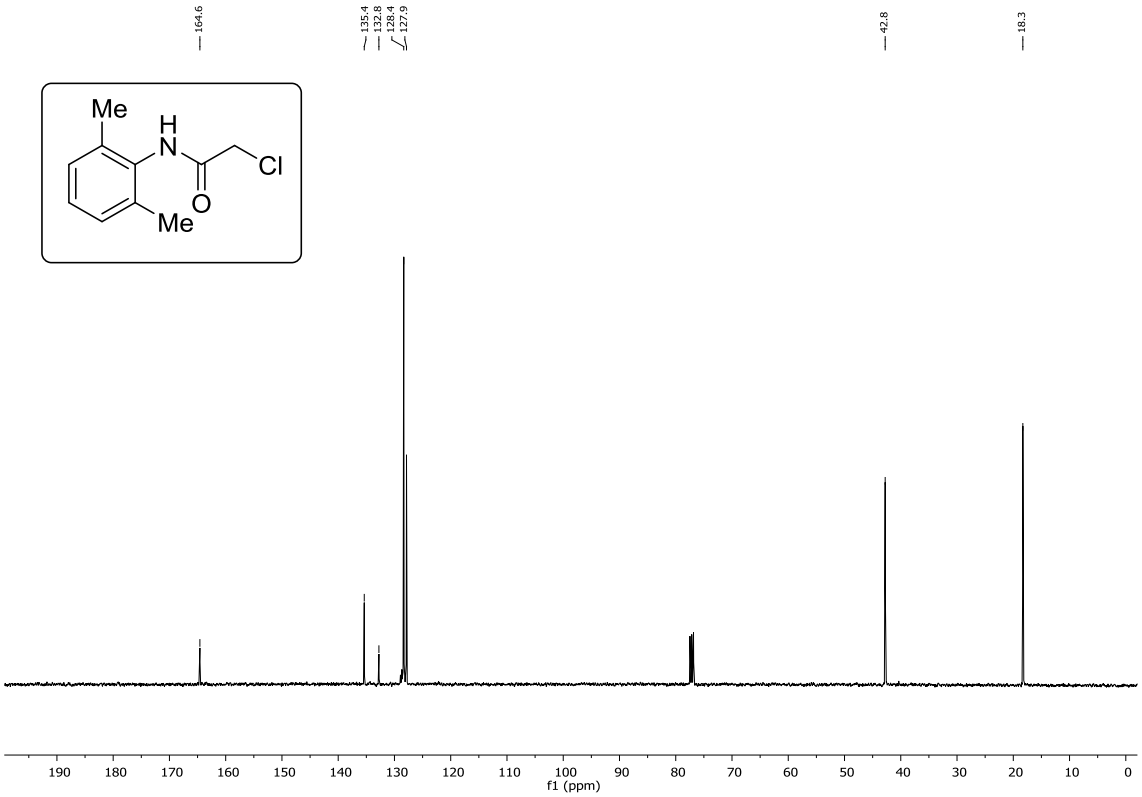


*lidocaina

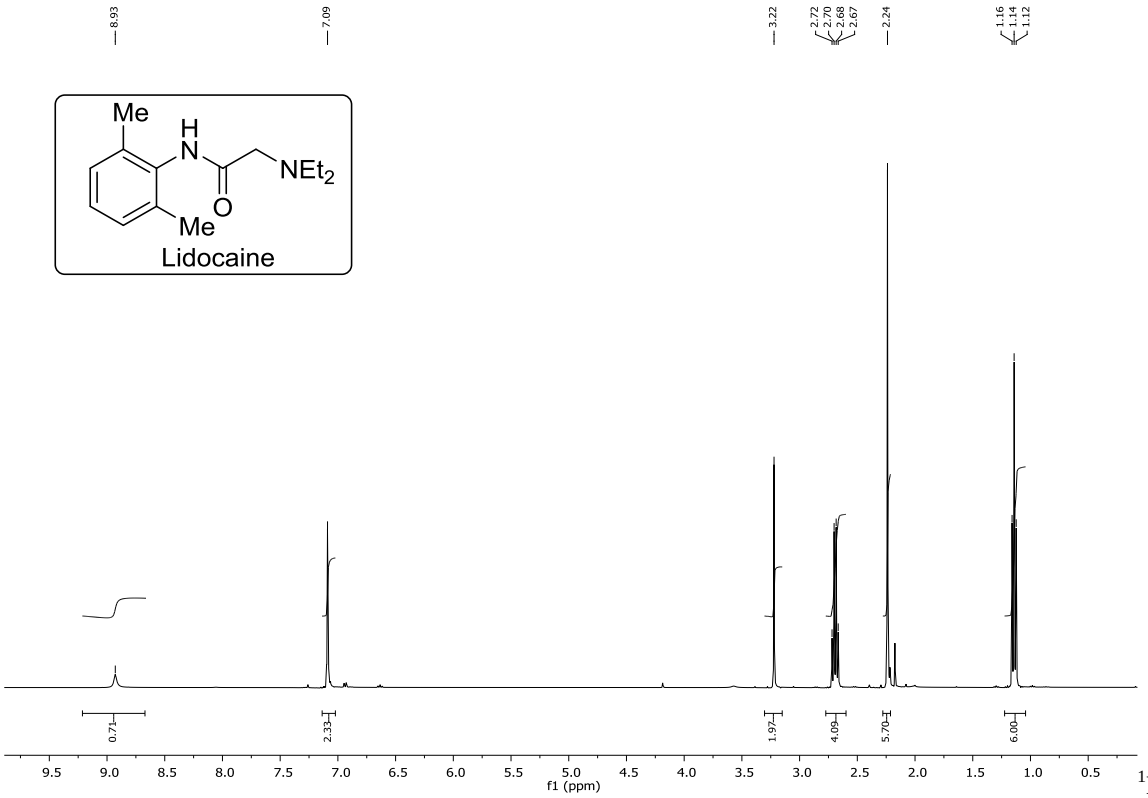
Nºbarridos: 10
Resolución: 2cm-1
Espectro: transmisión



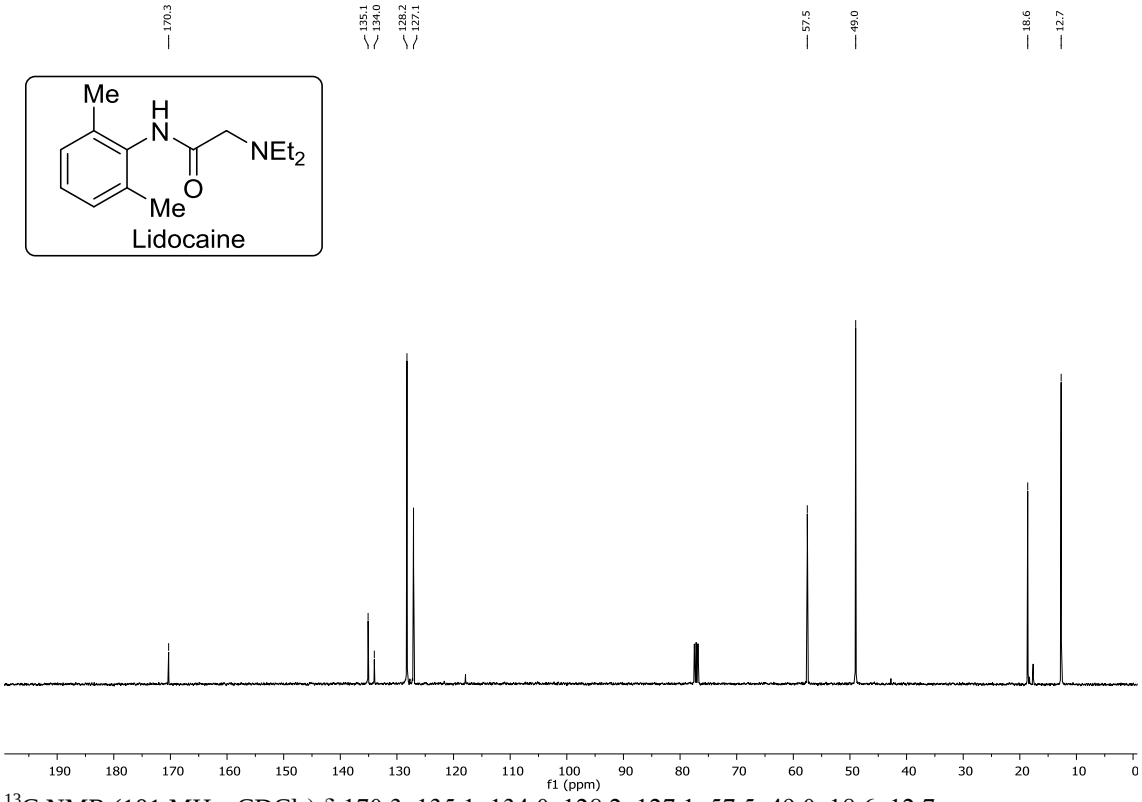
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.20 – 7.02 (m, 3H), 4.20 (s, 2H), 2.22 (s, 6H).



^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 135.4, 132.8, 128.3, 127.9, 42.8, 18.3.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 7.09 (s, 3H), 3.22 (s, 2H), 2.69 (q, *J* = 7.1 Hz, 4H), 2.24 (s, 6H), 1.14 (t, *J* = 7.1 Hz, 6H).



^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 135.1, 134.0, 128.2, 127.1, 57.5, 49.0, 18.6, 12.7.