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Synthesis of Novel phenoxy - isobutyric acid derivatives, Reaction of ketone under Bargellinic reaction conditions

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Abstract: In the present study, we report the synthesis of high quality alpha-phenoxy – isobutyric acid derivatives were carried out by the reaction. Phenol or substituted phenol dissolved with acetone excess amount of sodium hydroxide is added. After added chloroform, reaction mixture was refluxed for several hours to give alpha-phenoxy – isobutyric acid. The isolated acid was treated with thionyl chloride and its corresponding alchol to produce alpha - phenoxy isobutyric acid derivatives. We summarized the synthetic methodologies, yield, structural characteristics (NMR, Mass spectrum and C, H, N analysis) in their properties.
Key words: Ketone under Bargellinic reaction**.**

Introduction

The Bargellinic reaction in which phenol is condensed with acetone and chloroform in the presence of strong base to produce a sterically hindered α-phenoxy–isobutyric acid derivatives[1]. The synthesis of α-phenoxy – isobutyric acid derivatives strategy utilizes the Bargellinic reaction as the key bond forming step[2]. Several compounds were prepared by this route. The mechanism for this unusual condensation reaction was investigated[3]. Synthetic tool in organic synthesis and various nucleophiles and ketones have been employed in place of classic form. In this manner it has potentially been a constructive lead for the organic chemists. Generally Bargellinic type reaction dichloroepoxide intermediate are formed by the reaction of chloroform and ketones which are potentially active toward regioselective[4] nucleophile attack (scheme -1). The recent years have witnessed an increased activity in the area of α-phenoxy– isobutyric acid derivatives synthesis. α-phenoxy – isobutyric acid derivatives are persistent free radicals that exhibit remarkable stability primarily due to the absence of dimerization and disproportionation[5]. Their unique properties have sparked considerable interest from theoretical, chemicals and biological standpoints[6].

Experimental

Liquid substances were distilled prior to use. Melting points were uncorrected. 1HNMR spectra were measured on a Bruker Avance 400 (400MHz) spectrometer using TMS as the internal standard. Elemental analysis were measured on a (HERAEUS CHNO, Rapid) analyzer. Sonication were performed in Shanghi

Branson- CQX ultrasonic cleaner (with a frequency of 25KHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40KHz, 59 KHz and nominal power 250 W Shanghai Kudos ultrasonic Instrument Co., Ltd.) The reaction flask were located in the cleaner where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

Preparation-1:

The preparation of α-phenoxy isobutyric acid derivatives (scheme-1) phenol (21.2mmol), acetone (20mL), Sodium hydroxide 215mmol) were mixed in a 50mL round bottomed flask. The reaction mixture was stirred at room temperature for a period of 0.5hrs. A mixture chloroform 127 mmol and acetone 10mL were added over a period of 3 hrs. Exothermic were observed controlled the reaction mixture below 55°C. The reaction mixture was stirred at 53-55°C for 40-52 hrs. After completed the reaction solvent was distilled out under reduced pressure. The resulting suspension was quenched with 40 mL water, the reaction mixture was extracted with diethylether (3x10mL). The organic layer was discarding. The obtained aqueous layer to added 2N hydrochloric acid adjusted the pH= 3 to 4. The solid was filtered and give the crude product solid which was separated by column chloromatography on silica (200-300mesh), eluted with ethyl acetate and n-hexane (incorporated in Table-1).

Preparation -2:

The preparation of α-phenoxy isobutyric acid ester derivatives (scheme-2) α-phenoxy isobutyric acid (preparation-1) (1.87mmol), thionyl chloride 5mL were added then reflux for 3 hrs. The reaction mixture was distilled out at reflux temperature. The resulting suspension was quenched with benzene 5mL the reaction mixture was distilled out at reflux temperature to remove the traces of thionyl chloride. The resulting mixture was charged isopropanol (2mL) and pyridine (1.83mmol) the reaction mixture was heated to reflux for 0.5hrs at 65°C. The reaction mixture was cooled to room temperature. The reaction mixture was extracted with diethylether (3x10mL). The combined organic layers were washed aqueous bicarbonate (NaHCO3) solution and brine, dried over anhydrous magnesium sulfate for 2 hours and filtered; diethyl ether was evaporated under reduced pressure to give the pure product (incorporated in table-1).

(**1**). Melting point 95-97°C. ^{1}H NMR (400MHz, $CDCl_3$), §12.1-11.5 (broad, s, 1H), 7.2-7.00 (d, 11.2Hz, 2H), 6.9-6.7 (t, 12Hz, 2H) 6.5 (t, 9.2Hz, 1H), 2.7 (s, 12H); m/z : 266, 265, 251, 248, 248, 238, 236, 221, 206, 179, 173, 134, 116, 93, 87, 65, 60, 45, 30, 28, 18; Anal. Calcd for $C_{14}H_{18}O_5$: C 63.16, H 6.77; found C 63.19, H 6.79;

(**2**). Melting point 112°C. ^{1}H NMR (400MHz, $CDCl_3$), §11.8-11.2 (broad, s, 1H), 7.4-7.3(d, 9.5Hz, 2H), 7.2-7.1(d, 10.1Hz, 2H), 2.7 (s, 12H), 2.3(q, 2H), 1.8(t, 3H); m/z : 322, 307, 293, 277, 262, 235, 219, 191, 190, 173, 149, 132, 131, 103, 87, 62, 60, 57, 45, 29, 15; Anal. Calcd for $C_{17}H_{22}O_6$: C 63.35, H 6.83; found C 63.39, H 6.92;

(**3**).Melting point 126-127°C. ^{1}H NMR (400MHz, $CDCl_3$), §12.0-11.5 (broad, s, 1H), 7.5-7.3 (d, 10.2Hz, 4H), 7.2(d, 9.5Hz, 2H), 7.1-7.00(t, 12.00Hz, 2H), 6.9(t, 1H), 2.6(s, 12H); m/z: 355, 325, 293, 267, 265, 238, 181, 173, 163, 153, 132, 105, 103, 77, 71, 66, 45, 28, 15; Anal. Calcd for $C_{21}H_{22}O_6$: C 68.11, H 5.94; found C 68.15, H 5.94;

4). Melting point 135-138°C. ^{1}H NMR (400MHz, $CDCl_3$), §11.9-11.4 (broad, s, 1H), 7.5-7.3(d, 9.3Hz, 2H), 7.3-7.1(d, 10.5Hz, 2H), 2.7(s, 12H), 2.4(t, 2H), 2.3(m, 2H), 2.1-2.00(s, 4H), 1.8(t, 3H); m/z: 364, 349, 319, 318, 304, 293, 277, 265, 232, 191, 173, 165, 132, 99, 87, 71, 60, 46, 45, 28, 15; Anal. Calcd for $C_{20}H_{28}O_6$: C 65.93, H 7.69; found C 65.94, H 7.65;

(**5**). Melting point 141-143°C. ^{1}H NMR (400MHz, $CDCl_3$), §12.1-11.5(broad, s, 1H), 7.5-7.3(d, 10.2Hz, 2H), 7.2-7.00(d, 9.2Hz, 2H), 2.7(s, 12H), 2.4(t, 2H), 2.3(m, 2H), 1.9(broad, s, 8H), 1.7(t, 3H); m/z: 392, 347, 346, 332, 305, 293, 265, 260, 219, 173, 132, 127, 99, 87, 60, 46, 45; Anal. Calcd for $C_{22}H_{32}O_6$: C 67.35, H 8.16; found C 67.40, H 8.19;

(**6**). Melting point 105-106°C. ^{1}H NMR (400MHz, $CDCl_3$), §11.9-11.2 (broad, s 1H), 7.4-7.3 (d, 9.5Hz, 2H), 7.2-7.1(d, 10.1Hz, 2H), 2.7(s, 12H), 2.3(s, 3H); m/z: 308, 293, 265, 263, 262, 248, 221, 200, 176, 173, 135, 108, 87, 60, 46, 45, 43, 15; Anal. Calcd for $C_{16}H_{20}O_6$: C 62.34, H 6.49; found C 62.32, H 6.48;

(**7**). Melting point 120-121°C. ^{1}H NMR (400MHz, $CDCl_3$), §11.9-11.4 (broad, s 1H), 7.5-7.2 (d, 9.3Hz, 2H), 7.2-7.00(d, 9.8Hz, 2H), 2.7(s, 12H), 2.3(t, 2H), 1.9(m, 2H), 1.7(t, 3H); m/z: 336, 306, 291, 265, 249, 204, 200, 173, 163, 132, 87, 71, 45, 30, 28; Anal. Calcd for $C_{18}H_{24}O_6$: C 64.29, H 7.14; found C 64.26, H 7.17;

(**8**). Melting point 132-133°C. ^{1}H NMR (400MHz, $CDCl_3$), §12.1-11.2 (broad, s, 1H), 7.5-7.3 (d, 9.3Hz, 2H), 7.3-7.1(d, 10.5Hz, 2H), 2.7(s, 12H), 2.4(t, 2H), 1.9(m, 2H), 1.8-1.6(m, 2H), 1.4(t, 3H); m/z: 350, 320, 305, 265, 263, 218, 200, 177, 173, 150, 132, 87, 85, 45, 30, 28 Anal. Calcd for $C_{19}H_{26}O_6$: C 65.14, H 7.23; found C 65.12, H 7.24;

(**9**). Melting point 150°C. ^{1}H NMR (400MHz, $CDCl_3$), §12.5-11.5 (broad, s, 1H), 7.9(s, 1H), 7.7-7.5(d, 1H), 7.4(d, 1H), 7.3-7.20(d, 2H), 7.00-6.9(d, 2H), 2.7(s, 12H); m/z: 411, 381, 376, 366, 324, 279, 267, 210, 203, 173, 146, 132, 87, 45, 36, 30, 28: Anal. Calcd for $C_{20}H_{20}O_5Cl_2$: C 65.71, H 4.87; found C 65.72, H 4.89;

(**10**). Melting point 145°C ^{1}H NMR (400MHz, $CDCl_3$), §12.5-11.9 (broad, s, 1H), 7.9-7.8(d, 2H), 7.7-7.6(t, 1H), 7.5-7.3(d, 2H), 7.2-7.00(d, 2H) 2.6(s, 12H); m/z: 411, 381, 376, 366, 324, 279, 267, 210, 203, 173, 146, 132, 87, 45, 36, 30, 28: Anal. Calcd for $C_{20}H_{20}O_5Cl_2$: C 65.71, H 4.87; found C 65.72, H 4.88;

(**11**). Melting point 136°C. ^{1}H NMR (400MHz, $CDCl_3$), §12.5-11.9(broad, s, 1H), 7.5-7.4(d, 2H), 7.2-7.0(d, 2H), 3.1(m, 1H), 2.6(s, 12H), 2.5-2.3(q, 4H) 2.00-1.8(br, s, 6H); m/z: 376, 331, 293, 289, 265, 244, 203, 176, 173, 132, 111, 87, 83, 45, 28: Anal. Calcd for $C_{21}H_{28}O_6$: C 67.02, H 7.45; found C 67.05, H 7.48;

(**12**) Melting point 185°C. ^{1}H NMR (400MHz, $CDCl_3$); § 7.2-7.00(d, 11.2Hz, 2H), 6.9-6.7(t, 12Hz, 2H) 6.5(t, 9.2Hz, 1H), 5.2(m, 1H), 2.8(s, 12H); 1.9(d, 6H); m/z: 308, 265, 220, 215, 179, 174, 153, 134, 129, 88, 66, 43, 28; Anal. Calcd for $C_{17}H_{24}O_6$: C 66.23, H 7.79; found C 66.25, H 7.76;

(**13**) Melting point 206°C. ^{1}H NMR (400MHz, $CDCl_3$), § 7.4-7.3(d, 9.5Hz, 2H), 7.2-7.1(d, 10.1Hz, 2H), 4.1(s, 3H), 2.7(s, 12H) 2.3(q, 2H), 1.8(t, 3H); m/z: 336, 321, 305, 279, 277, 214, 202, 187, 149, 134, 122, 59, 57, 31, 15; Anal. Calcd for $C_{18}H_{24}O_6$: C 64.29, H 7.14; found C 64.32, H 7.16;

(**14**) Melting point 191-193°C. ^{1}H NMR (400MHz, $CDCl_3$), §7.5-7.3(d, 10.2Hz, 4H), 7.2(d, 9.5Hz, 2H), 7.1-7.0(t, 12.00Hz, 2H), 6.9(t, 1H), 3.9(q, 2H), 2.67(s, 12H), 1.9 (t, 3H); m/z: 398, 353, 325, 321, 293, 267, 239, 201, 197, 170, 159, 131, 105, 77, 73, 45; Anal. Calcd for $C_{23}H_{26}O_6$: C 69.35, H 6.53; found C 69.36, H 6.55;

(**15**) Melting point 215°C. ^{1}H NMR (400MHz, $CDCl_3$); § 7.5-7.3(d, 9.3Hz, 2H), 7.3-7.1(d, 10.5Hz, 2H), 5.2(m, 1H), 2.7(s, 12H), 2.4(t, 2H), 2.3 (m, 2H), 2.1-2.00(s, 4H), 1.8(t, 3H), 1.5 (d, 6H); m/z: 406, 347, 308, 307, 273, 233, 215, 191, 173, 164, 145, 99, 88, 59; Anal. Calcd for $C_{23}H_{34}O_6$: C 67.98, H 8.37; found C 67.99, H 8.39;

(**16**) Melting point 221°C. ^{1}H NMR (400MHz, $CDCl_3$) §7.5-7.3(d, 10.2Hz, 2H), 7.2-7.00(d, 9.2Hz, 2H), 3.9(q, 2H), 2.7(s, 12H), 2.4(t, 2H), 2.2-2.00(m, 2H), 1.9(broad, s, 8H), 1.7(t, 3H), 1.6(t, 3H); m/z: 420, 375, 293, 289, 228, 260, 219, 201, 192, 160, 131, 127, 115, 74, 45; Anal. Calcd for $C_{24}H_{36}O_6$: C 68.57, H 8.57; found C 68.59, H 8.61;

(**17**) Melting point 199°C. ^{1}H NMR (400MHz, $CDCl_3$), §7.4-7.3(d, 9.5Hz, 2H), 7.2-7.1(d, 10.1Hz, 2H), 4.2(t, 2H), 2.7(s, 12H), 2.3(s, 3H), 1.8(t, 3H); m/z: 336, 293, 291, 256, 205, 201, 176, 160, 135, 131, 108, 74, 45, 43; Anal.Calcd for $C_{18}H_{24}O_6$:C 64.29, H 7.14; found C 64.30, H 7.17;

(**18**) Melting point 208°C. ^{1}H NMR (400MHz, $CDCl_3$); § 7.5-7.2(d, 9.3Hz, 2H), 7.2-7.00(d, 9.8Hz, 2H), 4.1(s, 3H), 2.7(s, 12H), 2.3(t, 2H), 1.9(m, 2H), 1.7(t, 3H); m/z: 350, 319, 290, 279, 233, 204, 187, 163, 146, 136, 117, 71, 60, 31; Anal. Calcd for $C_{19}H_{26}O_6$: C 65.14, H 7.43; found C 65.18, H 7.47;

(**19**) Melting point 222°C. ^{1}H NMR (400MHz, $CDCl_3$), § 7.5-7.3(d, 9.3Hz, 2H), 7.3-7.1(d, 10.5Hz, 2H), 4.1(s, 3H), 2.7(s, 12H), 2.4(t, 2H), 2.3(m, 2H), 2.1-2.00(m, 2H), 1.5(t, 3H); m/z: 364, 333, 306, 291, 247, 218, 187, 177, 150, 146, 117, 73, 48, 31; Anal. Calcd for $C_{20}H_{28}O_6$: C 65.93, H 7.69; found C 65.94, H 7.67;

(**20**) Melting point 241°C. ^{1}H NMR (400MHz, $CDCl_3$), § 7.9 (s, 1H), 7.7-7.5(d, 1H), 7.3(d, 1H) 7.2-7.1(d, 2H), 7.00-6.8(d, 2H), 4.2(m, 1H), 2.7(s, 12H), 1.7(d, 6H); m/z: 453, 418, 394, 365, 350, 308, 279, 238, 215, 174, 145, 103, 88, 59, 36; Anal. Calcd for $C_{23}H_{26}O_5Cl_2$: C 60.06, H 5.74; found C 60.03, H 5.71;

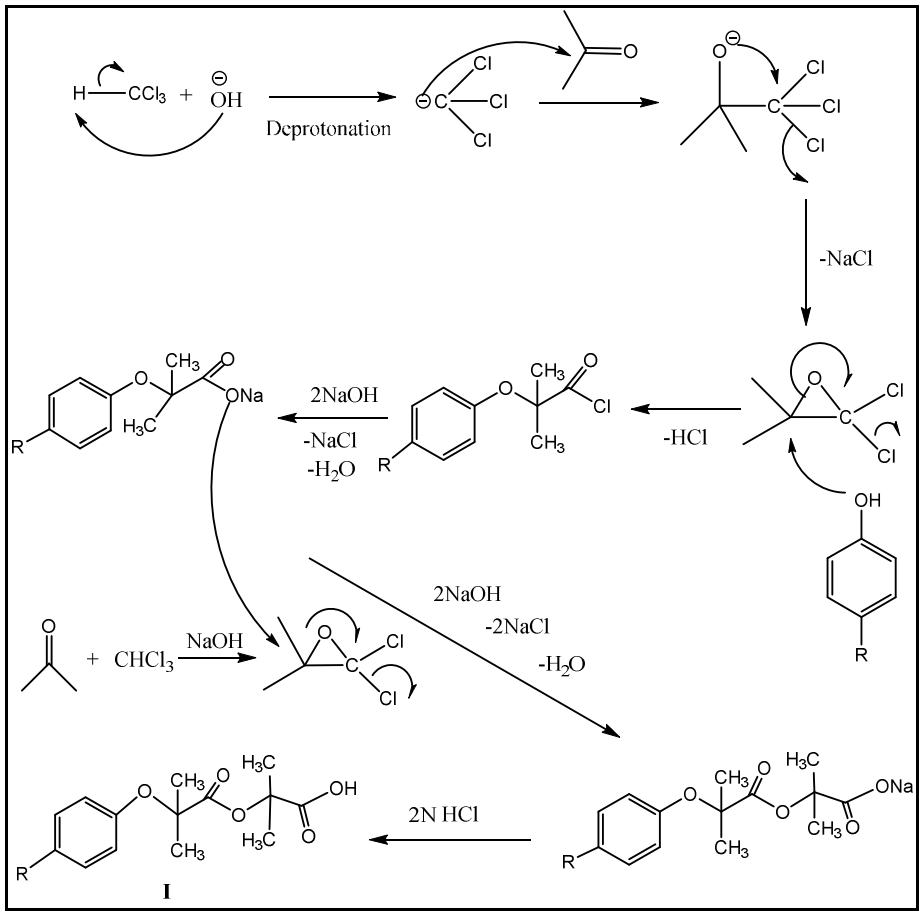
(**21**) Melting point 246°C. ^{1}H NMR (400MHz, $CDCl_3$); §7.9-7.8(d, 2H), 7.7-7.6(t, 1H), 7.5-7.3(d, 2H), 7.2-7.00(d, 2H), 3.9(q, 2H), 2.6(s, 12H), 1.8(t, 3H); m/z: 439, 394, 365, 308, 279, 265, 239, 238, 201, 200, 174, 160, 131, 74, 45; Anal. Calcd for $C_{22}H_{24}O_5Cl_2$: C 60.15, H 5.47; found C 60.18, H 5.49;

(**22**) Melting point 233°C. ^{1}H NMR (400MHz, $CDCl_3$), §7.5-7.4(d, 2H), 7.2-7.0(d, 2H), 4.2(m, 1H), 3.1(m, 1H), 2.6(s, 12H), 2.5-2.2(q, 4H), 2.00-1.8(br, s, 6H), 1.7(d, 6H); m/z: 418, 359, 330, 307, 273, 244, 215, 203, 176, 174, 145, 111, 88, 59, 28; Anal. Calcd for $C_{24}H_{34}O_6$: C 68.90, H 8.13; found C 68.92, H 8.15;

Result and discussions:

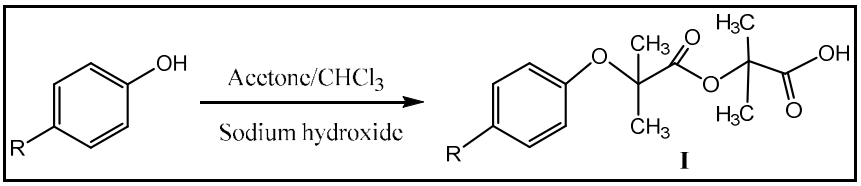
In the present study synthesis of α-phenoxy – isobutyric acid derivatives and esters was our initial objective. With the ultimate goal of producing pure α-phenoxy – isobutyric acid and its esters produced in the Bargellinic reaction with unsymmetrical ketones[7]. It is an example of the Bargellinic reaction in which a ketone, nucleophile and chloroform react in the presence of a strong base. Deprotonation of the chloroform by sodium hydroxide followed by nucleophile attack the ketone yields dichloroepoixde. The hindered O-C bond is formed via regioselective opening by the nucleophile an aromatic alcohol substituted phenol in the present example[8]. An aromatic alcohol would be close to the lactone via the acid chloride subsequently hydrolysis of the lactones in the strong basic medium leads to the observed products. The excess moles of acetone, chloroform and base then acid treatment to get the observed product (**I**)[9].

Mechanism:

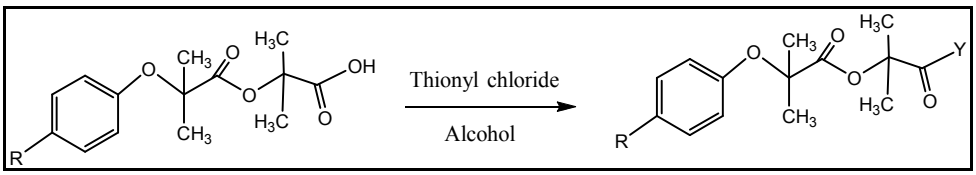


The fundamental reaction is phenol or substituted phenol (Aldrich chemicals, 98% pure) is dissolved in anhydrous acetone and then excess amount of sodium hydroxide flake is added (scheme-1)[10]. The corresponding sodium phenylate precipitates refluxing is affected and then excess amount of chloroform diluted with anhydrous acetone is added and the resulting mixture is refluxed for 40-52 hours. Normally these reaction 10 to 12 equivalent sodium hydroxides were used. After complete the reaction[11], acetone is evaporated then added water and aqueous phase is washed with ether then followed by acidification (2N HCl). During 2N hydrochloric acid addition solid is thrown out. Adjusted the pH=3-4 stir the reaction mixture for 1 hour at room temperature. The solid obtained is filtered and given water wash and air dried[13]. The solid obtained is passed through a column chromatography used ethylacetate and n-hexane as eluvent (Example in table I).

Scheme-1:



Scheme-2:



The standard procedure for the synthesis of α-phenoxy – isobutyric acid esters (scheme-2) involves the refluxing of a reaction mixture of an α-phenoxy – isobutyric acid derivatives and thionyl chloride, acid conversion into acid chloride then added concern alcohol with base (R=H, CH_3CO, C_2H_5CO, etc., The intermediate of acid chloride is unstable. A mixture of α-phenoxy – isobutyric acid derivatives with thionyl chloride is heated to reflux for 3-5 hours, distilled out slowly thionyl chloride at atmosphere distillation. Reaction is monitored by TLC after complete distillation benzene was charged. Benzene was distilled out to removes traces of thonly chloride. Charged alcohol (Y= Methoxy, Ethoxy, etc.,) and pyridine as inert solvent[14]. Stir the reaction mixture for 1-2 hours at 65°C, cool the reaction mixture at room temperature. The mixture is poured into a separator funnel and diethyl ether and water were added. Separated and the aqueous layers was extracted with diethyl ether three times. The combined diethyl ether extracts were dried over anhydrous sodium sulphate filtered and concentrated. The impurity was removed by acid base treatment to obtained α-phenoxy – isobutyric acid esters in table-I gave examples of p-carbonyl phenoxy isobutyric acid derivatives which are used as intermediate compounds for the preparation of the esters according to this invention[15].

Table-1:

Compound	R	Yield	Time/ hours	Compound	R	Y	Yield
1	H	82%	48	**12**	H	$OCH(CH_3)_2$	89%
2	CH_3CH_2CO	65%	45	**13**	CH_3CH_2CO	OCH_3	55%
3	C_6H_5CO	75%	44	**14**	C_6H_5CO	OC_2H_5	46%
4	$CH_3(CH_2)_4CO$	55%	52	**15**	$CH_3(CH_2)_4CO$	$OCH(CH_3)_2$	45%
5	$CH_3(CH_2)_6CO$	68%	41	**16**	$CH_3(CH_2)_6CO$	OC_2H_5	56%
6	CH_3CO	73%	48	**17**	CH_3CO	OC_2H_5	41%
7	$CH_3(CH_2)_2CO$	86%	41	**18**	$CH_3(CH_2)_2CO$	OCH_3	65%
8	$CH_3(CH_2)_3CO$	92%	47	**19**	$CH_3(CH_2)_3CO$	OCH_3	76%
9	3,4 Cl_2-C_6H_3CO	59%	48	**20**	3,4 Cl_2-C_6H_3CO	$OCH(CH_3)_2$	83%
10	2,6 Cl_2-C_6H_3CO	63%	45	**21**	2,6 Cl_2-C_6H_3CO	OC_2H_5	80%
11	Cyclohexyl-CO	79%	43	**22**	Cyclohexyl-CO	$OCH(CH_3)_2$	67%

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References

1. John T. Lai Hindered Amines Novel synthesis of 1,3,3,5,5 penta substituted 2-piperazinones J. Org. Chem. 1980, 45:754-755.

2. Mohammad Mahadavi, Mehdi Asadi, Mina Saeedi, Zahra Rezaei, Hooman Moghbel, Alireza Foroumadi, Abbas Shafiee, Letter 2012, 2521 – 2525.
3. Olofson R. A, Dougherty C. M., J. Am. Chem. SOC. 1973, 95: 581-582**.**
4. Senkus M. J, Am. Chem. SOC., 1946, 68:10.
5. Kuhl P, Muhlstadt M, Graefe J. Synthesis 1976, 825.
6. Weber W, Gokel G, Tetrahedron Lett., 1972, 1637.
7. Tabush I, Yoshida Z, Takahash N. J., Am. Chem. SOC., 1974, 96:3713.
8. Ma Z, Huang Q, Bobbitt J M. J. Org. Chem. 1993, 58: 4837-4843.
9. Lee T, D. Keana J. F. W., J. Org. Chem. 1975, 40:3145-3147.
10. Lai J, T Synthesis 1981, 754.
11. Kyrides, J. Am. Chem. Soc**.** 1937, 59: 208.
12. Butcher K. J. Hurst, J. Tetrahedron Lett. 2009, 50: 2497.
13. Ma Z, Bobbitt J. M. J. Org. Chem. 1991, 56: 6110-6114.

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