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Syntheses of Substituted tert. -Butyl (o-tolyl) -perpropionates

by

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tert.-Butyl β-(o-tolyl)-perpropionate 치환체들의 합성

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요 약

Chloromethylation, malonic ester 합성법 및 decarboxylation 에 의한 중간체들을 거친 *tert.*-butyl β-(o-tolyl)-perpropionate 치환체들의 합성을 기술하였다. 심하지 않은 치환기효과를 나타내는 bromo-, chloro- 및 methyl-기를 가진 중간체들은 좋은 수율로 얻어져서 목적한 바 과산화 ester 들을 얻었으나 nitro기를 가진 중간체는 극히 적은 수율로 얻어졌고 한편 센 electron donating effect 를 나타내는 group 로 치환된 toluene 들의 chloromethylation 은 polymerize 하는 결과를 가져 왔다.

Abstract

The syntheses of substituted *tert.*-butyl β-(o-tolyl)- perpropionates via intermediates obtained by chloromethylation, malonic syntheses and decarboxylation is described. The intermediates substituted with a group possessing moderate substituent effect such as bromo, chloro, and methyl group were obtained in good yields. The nitro-substituted intercmediate was obtained in poor yield. The chloromethylation of toluenes containing electron donating groups resulted in polymerization.

Introduction

Although it is known that various peresters can be used as a source of free radicals,[1-8] the syntheses of peresters have not been carried out extensively, owing principally to their unstability. In order to

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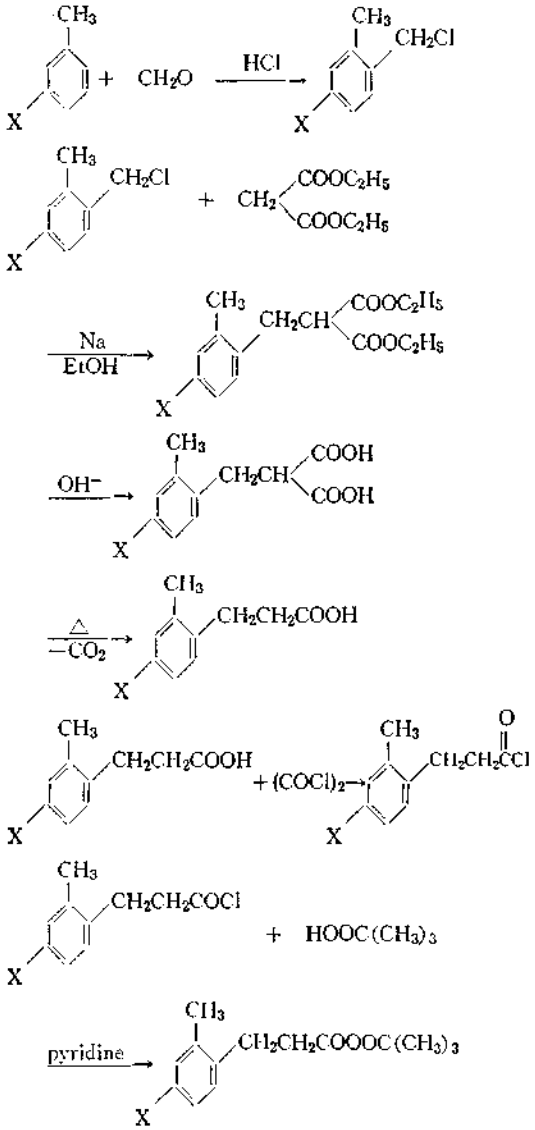
investigate the possibility of intra- and intermolecular hydrogen abstraction in the case of substituted β-(o-tolyl)-ethyl free radical, the effect(s) of substituents on the formation of the free radical and the relative ease of hydrogen abstraction in system, it has been attempted to synthesize substituted *tert.*-butyl β-(o-tolyl)-perpropionate from which the β-(o-tolyl)-ethyl radical can be generated by its decomposition. In this report the syntheses of substituted *tert.*-butyl- β-(o-tolyl)-perpropionates is described.

The general scheme for the preparation of the peresters is as follows:



The starting materials were 3- and 4-substituted toluenes, which were converted to substituted 2-methylbenzyl chloride by chloromethylation.[9,10] While the reaction conditions of the chloromethylation for *m*- and *p*-xylene were mild (60~70°C, 7 hours), *m*-bromo- and *m*-chloro-toluene required rather strong conditions (refluxed for 12 hours), and the yields of the latter were poor. The substituted 2-methylbenzyl chlorides were then converted to substituted diethyl (2-methylbenzyl)-malonates by malonic syntheses.[11] The esters were hydrolyzed with alkali and decarboxylated to form the corresponding substituted β-o-tolylpropionic acids, which were then converted to substituted β-o-tolylpropionyl chlorides. The syntheses of the intermediates described were generally straightforward and the yields were reasonable. For the final step, the acid chlorides were treated with *tert.*-butyl hydroperoxide in the presence of pyridine to obtain substituted *tert.*-butyl (β-o-tolyl)-perpropionates. In order to avoid the undesirable detonation of the peresters obtained, the purification of the peresters was carried out by liquid absorption chromatography on Florisil column rather than distillation.

For the purpose of synthesizing nitro-substituted *tert.*-butyl β-(o-tolyl)-perpropionate, a number of attempts to obtain the starting material, 2-methyl-5-nitrobenzyl chloride, were made. Chloromethylation of 4-nitrotoluene in concentrated hydrochloric acid media using formaldehyde was unsuccessful even under reflux for 48 hours. Among the various attempts the use of bis-chloromethzyl ether in 20% fuming sulfuric acid proved successful, although the yield of the desired 2-methyl-5-nitrobenzyl chloride was of the order of 5%. The indifference of 4-nitrotoluene to chloromethylation is obviously due to the strong deactivating effect of the nitro group. The fact that the lower yields of chloromethylation of *m*-bromo- and *m*-chlorotoluene previously mentioned are also to be ascribed to the deactivating influence of the halogen atom. An alternative method for the synthesis of nitro-substituted β-(o-tolyl)-perpropionate has been developed, which consists in the nitration of β-(o-tolyl)-propionic acid. However, the result of analysis indicated that two nitro groups had introduced into the phenyl ring, although the nitration was carried out under very mild condition.

On the contrary, the chloromethylation of compounds containing strong electron donators such as *m*-cresol

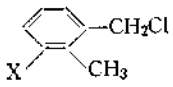
and *m*-methoxytoluene polymerized rapidly forming an undesirable viscous polymer. The chloromethylation of amino-, hydroxy- and methoxy-substituted toluenes have been unsuccessful.

Experimental

2, 5-Dimethylbenzyl chloride[9, 10] and substituted 2-methylbenzyl chlorides. ——A mixture of 106 g. (1 mole) of *p*-xylene, and equal weight(1.3 mole) of 37% formalin solution and 530 g. of conc. HCl was stirred vigorously for 7 hours at 60~70°, during which period a slow stream of HCl gas was introduced into the mixture. The mixture was then treated with water and extracted with diethyl ether. The ether was removed by evaporation and the remaining liquid was purified by vacuum distillation. 2, 4-Dimethyl-benzyl chloride, 2-methyl-4-chlorobenzyl chloride and 2-methyl-4-bromobenzyl chloride were prepared by the same method. The results of analysis, b. p. and yields of these compounds are listed in Table I.

TABLE I

Substituted-2-methylbenzyl Chldrides



X	B. p., °C(mm)	Yield%	Formula	Carbon (%)* Calcd.	Found	Hydrogen (%) Calcd.	Found	Chloride (%) Calcd.	Found
4-CH_3	42 (0.01)	71	$C_9H_{11}Cl$	69.90	69.54	7.17	7.08	22.93	23.09
5-CH_3	38~40 (0.05)	51	$C_9H_{11}Cl$	69.90	69.93	7.17	7.11	22.93	22.78
4-Cl	62~63 (0.30)	22	$C_8H_8Cl_2$	54.88	54.75	4.61	4.60	40.51	40.73
4-Br	63~64 (0.07)	18	C_8H_8BrCl	43.77	43.83	3.68	3.69	16.15	16.32

* All analyses in this report were carried out at Spang Microanalytical Laboratory, Ann Arbor, Michigan, U.S.A.

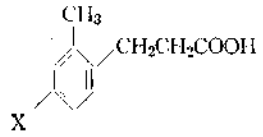
Diethyl (2, 5-dimethylbenzyl)-malonate and substituted-diethyl (2-methylbenzyl) malonates.——Using a modification of the method of Clemo and Swan,[11] 52 g. (0.32 mole) of diethyl malonate was added slowly with stirring to a warm solution of sodium ethylate prepared from 7.4 g. (0.32 mole) of sodium metal and 170 ml. of absolute ethyl alcohol. Into the mixture was added 50 g. (0.32 mole) of 2, 5-dimethylbenzyl chloride dropwise with vigorous stirring. In the first 5 min. the mixture changed to a milky white. After completion of the addition, which took ca. 15 min., the mixture was refluxed for 2 hours. The alcohol was removed by distillation and the residue was treated with ice-water. The solution formed two layers, and the aq. bottom layer was extracted with ether. The ether solution was then combined with the upper oil layer and dried over Na_2SO_4. The crude product was distilled in *vacuo*, b. p. 133~140° (0.20 mm.); yield 65 g. (72%). The other compounds of this series were prepared by a similar method. The b. p. (°C) and the yield of esters are as follows: diethyl(2-methylbenzyl)-malonate, 124~126°(0.05mm), 71%; diethyl(2, 4-dimethylbenzyl)-malonate, 111~113° (0.05 mm.), 73%; diethyl (2-methyl-4-chlorobenzyl)-malonate, 120~122° (0.05 mm.), 58%; diethyl (2-methyl-4-bromobenzyl)-malonate, 132° (0.05 mm.), 55%.

β-(-2,4-Dimethyl)-phenylpropionic acid and substituted-β-(2-methyl)-phenylpropionic acids. ——To 70 g. (0.25 mole) of diethyl (2, 4-dimethyl-benzyl)-malonate was added dropwise 56 g. (1 mole) of potassium hydroxide in 100 ml. of water. The mixture was then refluxed for 3 hours, during which period an additional 20 g. of potassium hydroxide pellets was added from time to time through the top of a condenser attached to the reaction flask in order to guarantee the hydrolysis. At the completion of the hydrolysis the solution was homogeneous. Acidifying the solution with conc. HCl at pH ca. 6 gave a white ppt of (2, 4-dimethyl)-benzyl-malonic acid. The crude dibasic acid was then decarboxylated by refluxing for 3 hours in the presence of 10% aq. sulfuric acid solution. Two recrystllizations first from 30% aq. acetic acid solution and two more from 30% ethyl

alcohol solution completed purification. The other compounds of this series were also prepared by the same method. The data of analysis, yield and m. p. are listed in Table II.

TABLE II.

Substituted β-o-Tolylpropionic Acids



X	M. P., °C	Yilds%[a]		Carbon%		Hydrogen%		Chlorine%		Bromine%	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
H	101	73	$C_{10}H_{12}O_2$	73.15	73.24	7.37	7.37				
4-CH_3	100.5~101	60	$C_{11}H_{14}O_2$	74.13	74.18	7.92	7.90				
5-CH_3	46 ~ 47	60	$C_{11}H_{14}O_2$	74.13	74.02	7.92	7.96				
4-Cl	81 ~ 82	60	$C_{10}H_{11}ClO_2$	60.46	60.50	5.58	5.48	17.85	17.97		
4-Br	79 ~ 80	68	$C_{10}H_{11}BrO_2$	49.41	49.45	4.56	4.64			32.87	32.70

(a) Calculated from the amount of diethyl(2-methylbenzyl)-malonates.

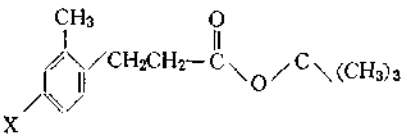
β-(2-Methyl-4-chloro)-phenylpropionyl chloride and substituted-β-(2-methyl)-phenylpropionyl chlorides.——To 6.2 g. (0.03 mole) of β-(2-methyl-)4-chloro)-phenylpropionic acid was added an excess amount (ca. 6.4 g., 0.05 mole) of oxalyl chloride (Eastman Organic Chemicals), and the mixture was refluxed for 3 hours. The ceasation of gas evolution indicated the completion of the reaction. The crude oil product was purified by vacuum distillation; colorless liquid, b. p. 80~82°C (0.05 mm.), yield 85%. The rest of propionyl chlorides were also prepared by the same method. The b. p. (°C) and the yield of the series of acid chlorides thus obtained are as follows:

β-o-tolypropionyl chloride, 76~78° (0.35 mm.), 80%; β-(2,5-dimethyl)-phenylpropionyl chloride, 122°(0.10 mm.), 81%; β-(2,4-dimethyl)-phenylpropionyl chloride, 82°(0.08 mm.), 75%; β-(2-methyl-4-bromo)-phenylpropionyl chloride, 116~118°(0.50 mm.), 53%.

***tert.*-Butyl(2-methyl-4-bromo)-phenyl-perpropionate and substituted-*tert.*-butyl(2-methyl)-phenylperpropionates.**——Into a mixture of 5.8 g. (0.022 mole) of β-(2-methyl-4-bromo)-phenylpropionyl chloride and an excess amount (ca. 5.4 g., 0.06 mole) of *tert.*-butyl hydroperoxide (Wallace and Tierman, Inc., Buffalo 5, N. Y.) in 30 ml. of *n*-pentane which was dried over sodium sulfate before use was added dropwise 1.74 g. (0.022 mole) of pyridine with gentle stirring at room temperature. White fumes were formed during the addition. The mixture was stirred for 12 hours at room temperature, during which time two layers separated. The upper *n*-pentane layer was treated with cold water, and then was washed twice with 35 ml. portions of 10% sulfuric acid, twice with 25 ml. portions of 10% sodium bicarbonate and finally twice with cold water. The product in *n*-pentane was purified by passing through a short column of Florisil (Floridin Co., Tallahassee, Florida) and eluted with *n*-pentane. After removing the pentane by distillation, the perester remained. The results of analysis and yields of peresters thus obtained are listed in Table III.

Table III

Substituted *tert.*-Butyl β-(o-tolyl)-perpropionates



X	Yield%	Formula	Carbon% Calcd.	Found	Hydrogen% Calcd.	Found	Chloring% Calcd.	Found	Bromide% Calcd.	Found
H	60	$C_{14}H_{20}O_3$	71.16	70.96	8.53	8.59				
4-CH_3	50	$C_{15}H_{22}O_3$	71.97	72.07	8.86	8.79				
5-Ch_3	50	$C_{15}H_{22}O_3$	71.97	71.80	8.86	8.77				
4-Cl	43	$C_{14}H_{19}ClO_3$	62.10	61.96	7.07	7.07	13.10	13.28		
4-Br	53	$C_{14}H_{19}BrO_3$	53.34	53.12	6.08	5.96			25.35	25.49

2-Methyl-5-nitrobenzyl chloride.——To a mixture of 20 g. of bis-chloromethyl ether and 50 g. of fuming sulfuric acid containing 20% sulfur trioxide was added 10 g. of *p*-nitrotoluene slowly with gentle stirring so as to the temperature of the mixture could not raise higher than 50°C. Completing the addition, the mixture was stirred overnight at room temperature. The mixture was treated with ice-water, and brown viscous solid obtained was purified by chromathography eluting with methyl alcohal, and was recrystalized from 50% aq. methyl alcohol several times, m. p. 57~58°; yield less than 5%.

Anal. Calcd. for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; Cl, 19.10; N, 7.55. Found: C, 51.77; H, 4.36; Cl, 19.20; N, 7.48.

Attempt to prepare β-(2-methyl-5-nitro)-phenylpropionic acid.——A solution of 10 g. of β-(o-tolyl)-propionic acid in 50 ml. carbon terachloride was added with stirring to a mixture consisting of 25 ml. of conc. sulfuric acid and 15 ml. of conc. nitric acid (70%, D=1.4). The temperature was maintained below 50°C and stirred for 30 minutes after completion of the addition without further heating. The mixture was then treated with ice-water and extracted from ether. The ether-carbon tetrachloride layer was then washed with cold water and 5% sodium bicarbonate solution several times. The usual working up gave 6g. of crude white solid. Recrystalized from 50% aq. alcohol solution. m. p. 142~144°; white rhombic crystals.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70: For $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.26; H, 3.93; N, 11.04.

The analyses proved that the compound above obtained is β-(2-methyldinitro)-phenylpropionic acid.

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References

(1) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp 509~511.

(2) S. G. Cohen and D. B. Sparrow, *J. Am. Chem. Soc.*, **72**, 611(1950).

(3) F. Strain et. al., *ibid.*, **72**, 1254(1950).

(4) A. T. Blomquist and A. F. Ferris, *ibid.*, **73**, 3408, 3412(1951).

(5) A. T. Blomquist and J. A. Bernstein, *ibid.*, **73**, 5546(1951).

(6) H. C. McBay and O. Tucker, *J. Org. Chem.*, **19**, 869(1954).

(7) W. Cooper, *J. Chem. Soc.*, 1340(1951); *ibid.*, 1180(1952).

(8) A. G. Davies and K. J. Hunter, *ibid.*, 1809 (1953).

(9) J. V. Brown and J. Nelles, *Ber.*, **17**, 1094 (1934).

(10) R. C. Fuson and C. H. McKeever, *Org. Reac.*, vol. I, pp 69(1942).

(11) G. R. Clemo and G. A. Swan., *J. Chem. Soc.*, 491(1949).