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Synthesis of 2,4-Substituted 3-Oxo-1-phenylcyclopentane-1-carboxylic Acids

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Abstract—A procedure has been developed for the synthesis of 2,4-substituted 3-oxo-1-phenylcyclopentan-1-carboxylic acids, and substituent effects on particular steps of the synthesis have been studied.

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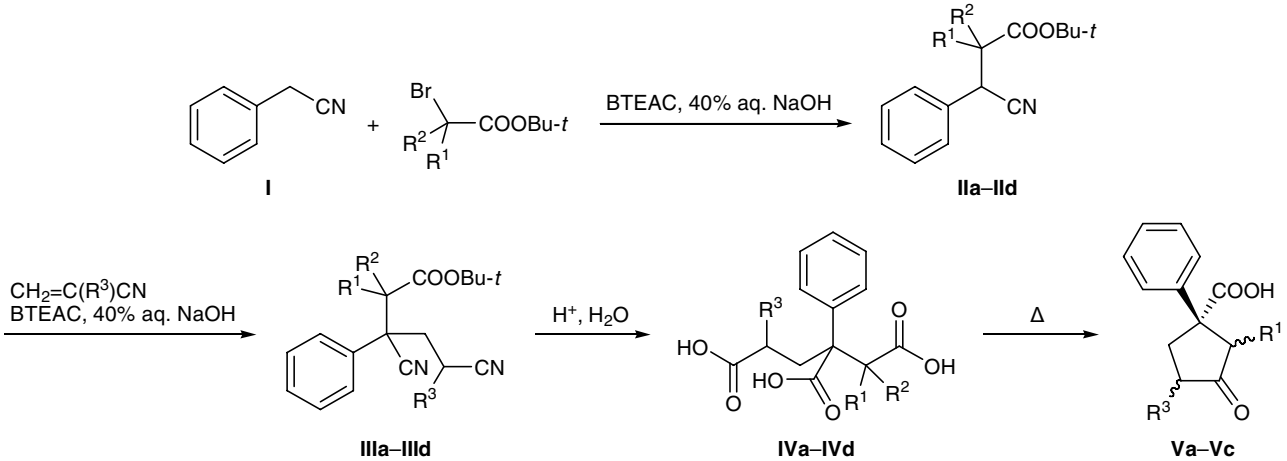
We previously developed a convenient procedure for the synthesis of 3-oxo-1-phenylcyclopentane-1-carboxylic acid via successive alkylation of phenylacetonitrile with *tert*-butyl chloroacetate and *tert*-butyl 3-chloropropanoate under conditions of phase-transfer catalysis, followed by the Dieckmann cyclization [1]. 2,4-Substituted 3-oxo-1-phenylcyclopentane-1-carboxylic acids are important starting compounds for the preparation of analogs of the antitumor antibiotic Sarcomycin [2–4] and antiviral antibiotic Amidinomycin [5]. With a view to improve the procedure for the preparation of such compounds and examine the effect of the R^1, R^2, and R^3 substituents on the reaction course, we have developed another version which differs from that described in [1]. In the second step, instead of alkylation with *tert*-butyl 3-chloropropanoate, we performed cyanoethylation with acrylonitrile and methacrylonitrile under conditions of phase-transfer catalysis (Scheme 1).

First, phenylacetonitrile was treated with *tert*-butyl bromoacetate, 2-bromopropionate, 2-bromo-2-methylpropionate, and 2-bromo-3-methylbutanoate in 40% aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride (BTEAC). The alkylation smoothly occurred to give compounds **IIa**–**IId**, regardless of the R^1 and R^2 substituent. The cyanoethylation of **IIa**–**IId** with acrylonitrile and methacrylonitrile was performed under analogous conditions. In this case, the

Scheme 1.



II, $R^1 = R^2 = H$ (**a**), Me (**c**); R^1 = Me, R^2 = H (**b**); R^1 = H, R^2 = *i*-Pr (**d**); **III**, **IV**, $R^1 = R^2$ = H, R^3 = Me (**a**); R^1 = Me, $R^2 = R^3$ = H (**b**); $R^1 = R^3$ = Me, R^2 = H (**c**); $R^1 = R^3$ = H, R^2 = *i*-Pr (**d**); **V**, R^1 = H, R^3 = Me (**a**); R^1 = Me, R^3 = H (**b**); $R^1 = R^3$ = Me (**c**).

substituent effect was obvious, and no reaction occurred with compound **IIc** (R^1 = R^2 = Me) even at elevated temperature. The hydrolysis of **IIIa**–**IIId** with hydrochloric acid was also smooth, but the subsequent pyrolysis of the corresponding tricarboxylic acids **IVa**–**IVd** strongly depended on the R^2 substituent: it did not occur with compound **IVd** (R^1 = R^3 = H, R^2 = Me_2CH). Our attempt to effect Dieckmann cyclization of compound **IIId** having the same substituents (R^1 = R^3 = H, R^2 = *i*-Pr) was also unsuccessful.

Thus we succeeded in synthesizing three new Sarcomycin analogs: 4-methyl-, 2-methyl-, and 2,4-dimethyl-3-oxo-1-phenylcyclopentane-1-carboxylic acids **Va**–**Vc**. Analysis of their ^{1}H NMR spectra showed that carboxylic acids **Va** and **Vb** are mixtures of *cis* and *trans* stereoisomers at a ratio of ~1:1. Protons in the methyl groups of the *trans* and *cis* isomers of **Va** give rise to two doublets centered at δ 1.05 and 1.13 ppm (J = 7.0 Hz); the corresponding signals of the *trans* and *cis* isomers of **Vb** appear at 0.65 and 1.15 ppm (J = 7.0 Hz). 2,4-Dimethyl-3-oxo-1-phenylcyclopentane-1-carboxylic acid (**Vc**) is a mixture of approximately equal amounts of four possible stereoisomers (δ, ppm: 0.60 d.d and 1.15 d.d, J = 7.0 Hz, for *trans*- and *cis*-2-CH_3; 1.05 d.d and 1.13 d.d, J = 7.0 Hz for *trans*- and *cis*-4-CH_3, respectively). The observed difference in the chemical shifts of the methyl protons originates from magnetically anisotropic effect of the aromatic ring [6].

Stereoisomers of compounds **Va**–**Vc** are unstable. In acidic or basic medium, an isolated individual stereoisomer is converted into a mixture of all possible isomers through the corresponding enol form.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-300 instrument at 300 MHz. Thin-layer chromatography was performed on Silufol UV-254 plates using acetone–hexane mixtures (A, 1:1; B, 1:2; C, 1:3; D, 3:2).

***tert*-Butyl 3-cyano-3-phenylpropanoates IIa–IId** were synthesized by the procedure described in [1].

Compound **IIa** (R^1 = R^2 = H). Yield 60%, bp 141–143°C (4 mm), mp 57–58°C, R_f 0.45 (C). ^{1}H NMR spectrum, δ, ppm: 1.20 s (9H, *t*-Bu), 2.62 d (2H, CH_2, J = 7.0 Hz), 4.05 t (1H, CH, J = 7.0 Hz), 7.20–7.30 m (5H, C_6H_5). Found, %: C 71.17; H 7.60; N 5.89. $C_{14}H_{17}NO_2$. Calculated, %: C 71.46; H 7.28; N 5.95.

Compound **IIb** (R^1 = CH_3, R^2 = H). Yield 70%, bp 137–138°C (3 mm), mp 44–45°C, R_f 0.48 (C). ^{1}H NMR spectrum, δ, ppm: 0.95 d and 1.24 d (3H, CH_3, J = 8.0 Hz), 1.23 s and 1.34 s (9H, *t*-Bu), 2.50–2.90 m (1H, CH), 3.79 d and 4.02 d (1H, CH, J = 8.0 Hz), 7.10–7.20 m (5H, C_6H_5). Found, %: C 73.40; H 7.50; N 5.85. $C_{15}H_{19}NO_2$. Calculated, %: C 73.47; H 7.75; N 5.71.

Compound **IIc** (R^1 = R^2 = CH_3). Yield 30%, bp 145–148°C (5 mm), R_f 0.50 (C). ^{1}H NMR spectrum, δ, ppm: 1.05 s (3H, CH_3), 1.25 s (3H, CH_3), 1.44 s (9H, *t*-Bu), 4.25 s (1H, CH), 7.20–7.30 m (5H, C_6H_5). Found, %: C 74.20; H 7.95; N 5.20. $C_{16}H_{21}NO_2$. Calculated, %: C 74.13; H 8.10; N 5.40.

Compound **IId** (R^1 = H, R^2 = $(CH_3)_2CH$]. Yield 25%, mp 152–153°C, R_f 0.53 (C). ^{1}H NMR spectrum, δ, ppm: 1.11 d (6H, CH_3, J = 7.0 Hz), 1.25 s (9H, *t*-Bu), 2.10–2.80 m (2H, CHCHCO), 4.06 d (1H, CHCN, J = 10.0 Hz), 7.20–7.35 m (5H, C_6H_5). Found, %: C 74.30; H 8.30; N 5.00. $C_{17}H_{23}NO_2$. Calculated, %: C 74.70; H 8.40; N 5.10.

***tert*-Butyl 3,5-dicyano-3-phenylpentanoates IIIa–IIId** (*general procedure*)**.** Acrylonitrile or methacrylonitrile, 0.3 mol, was added at 35°C to a mixture of 0.3 mol of compound **IIa**–**IId**, 100 ml of 40% aqueous sodium hydroxide, 150 ml of benzene, and 1.15 g (5 mmol) of benzyltriethylammonium chloride. The mixture was heated for 4 h at 50°C, the organic phase was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated, and the residue was recrystallized from hexane or carbon tetrachloride.

Compound **IIIa** (R^1 = R^2 = H, R^3 = CH_3). Yield 58%, mp 67–68°C, R_f 0.40 (C). ^{1}H NMR spectrum, δ, ppm: 1.28 s (9H, *t*-Bu), 1.45 d (3H, CH_3, J = 7.0 Hz), 2.20–2.80 m (3H, CH_2CH), 2.95 s (2H, 5-CH_2), 7.25–7.45 m (5H, C_6H_5). Found, %: C 72.50; H 7.10; N 9.70. $C_{18}H_{22}N_2O_2$. Calculated, %: C 72.48; H 7.38; N 9.39.

Compound **IIIb** (R^1 = CH_3, R^2 = R^3 = H). Yield 95%, mp 93–94°C, R_f 0.42 (C). ^{1}H NMR spectrum, δ, ppm: 1.28 s (9H, *t*-Bu), 1.45 d (3H, CH_3, J = 7.0 Hz), 1.95–2.50 m (4H, C^4H_2, C^5H_2), 2.94 q (1H, C^2H, J = 7.0 Hz), 7.25–7.45 m (5H, C_6H_5). Found, %: C 72.15; H 7.50; N 9.63. $C_{18}H_{22}N_2O_2$. Calculated, %: C 72.48; H 7.38; N 9.39.

Compound **IIIc** (R^1 = R^3 = CH_3, R^2 = H). Yield 36%, mp 137–138°C, R_f 0.30 (C). ^{1}H NMR spectrum, δ, ppm: 1.15 d (3H, CH_3, J = 7.0 Hz), 1.25 s (9H, *t*-Bu), 1.52 d (3H, CH_3, J = 7.0 Hz), 1.90–2.60 m (3H,

CH_2CH), 2.9 q (1H, C^2H, J = 7.0 Hz), 7.05–7.20 m (5H, C_6H_5). Found, %: C 69.00; H 7.28; N 8.80. $C_{19}H_{24}N_2O_2$. Calculated, %: C 68.67; H 7.20; N 8.40.

Compound **IIId** (R^1 = R^3 = H, R^2 = $(CH_3)_2CH$]. Yield 95%, mp 115–117°C, R_f 0.49 (B). ^1H NMR spectrum, δ, ppm: 1.18 s (9H, *t*-Bu), 1.05 d and 1.21 d (6H, CH_3, J = 7.0 Hz), 1.60–2.90 m (6H, CH_2CH_2, CHCH), 7.35–7.55 m (5H, C_6H_5). Found, %: C 73.80; H 8.10; N 8.30. $C_{20}H_{26}N_2O_2$. Calculated, %: C 73.60; H 7.97; N 8.58.

1,4-Substituted 2-phenylbutane-1,2,4-tricarboxylic acids IVa–IVd (*general procedure*). A mixture of 0.1 mol of compound **IIIa–IIId** and 150 ml of concentrated hydrochloric acid was heated for 8 h at the boiling point. The mixture was cooled and extracted with diethyl ether, the extract was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was recrystallized from water.

Compound **IVa** (R^1 = R^2 = H, R^3 = CH_3). Yield 84%, mp 175–176°C, R_f 0.49 (D). ^1H NMR spectrum, δ, ppm: 0.82 d and 1.05 d (3H, CH_3, J = 7.0 Hz), 1.60–2.90 m (3H, CH_2CH), 3.16 s (2H, CH_2), 7.35–7.50 m (5H, C_6H_5), 11.65 s (3H, COOH). Found, %: C 59.80; H 5.70. $C_{14}H_{16}O_6$. Calculated, %: C 60.00; H 5.71.

Compound **IVb** (R^1 = CH_3, R^2 = R^3 = H). Yield 90%, mp 161–162°C, R_f 0.5 (A). ^1H NMR spectrum, δ, ppm: 0.92 d and 1.13 d (3H, CH_3, J = 7.0 Hz), 1.85–2.40 m (4H, CH_2CH_2), 2.97 q (1H, CH, J = 7.0 Hz), 7.25–7.40 m (5H, C_6H_5), 11.98 s (3H, COOH). Found, %: C 60.25; H 5.74. $C_{14}H_{16}O_6$. Calculated, %: C 60.00; H 5.71.

Compound **IVc** (R^1 = R^3 = CH_3, R^2 = H). Yield 60%, mp 185–186°C, R_f 0.52 (D). ^1H NMR spectrum, δ, ppm: 0.89 d and 1.17 d (6H, CH_3, J = 7.0 Hz), 1.75–2.85 m (3H, CH_2CH), 3.22 q (1H, CH, J = 7.0 Hz), 7.25–7.40 m (5H, C_6H_5), 11.15 s (3H, COOH). Found, %: C 61.30; H 6.00. $C_{15}H_{18}O_6$. Calculated, %: C 61.20; H 6.10.

Compound **IVd** (R^1 = R^3 = H, R^2 = $(CH_3)_2CH$]. Yield 95%, mp 110–111°C, R_f 0.50 (D). ^1H NMR spectrum, δ, ppm: 1.05 d and 1.19 d (6H, CH_3, J = 7.0 Hz), 1.60–3.50 m (6H, CH_2CH_2, CHCH), 7.30–7.50 m (5H, C_6H_5), 12.45 s (3H, COOH). Found, %: C 62.00; H 7.00. $C_{15}H_{18}O_6$. Calculated, %: C 62.30; H 6.60.

2,4-Substituted 3-oxo-1-phenylcyclopentane-1-carboxylic acids Va–Vc (*general procedure*). Compound **IVa–IVc**, 0.1 mol, was heated for 30 min at 250–270°C under nitrogen. The resulting material was cooled and dissolved in 50 ml of 8% aqueous sodium hydrogen carbonate. The solution was washed with several portions of diethyl ether, the aqueous phase was acidified with 10% hydrochloric acid to pH 2–3, the oily material was extracted into diethyl ether, and the extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from carbon tetrachloride.

Compound **Va** (R^1 = H, R^3 = CH_3). Yield 68%, mp 102–103°C, R_f 0.59 (A). ^1H NMR spectrum, δ, ppm: 1.05 d.d and 1.13 d.d (3H, 4-CH_3, J = 7.0 Hz), 1.85–3.60 m (5H, 2-H, 4-H, 5-H), 7.20–7.45 m (5H, C_6H_5), 10.05 s (1H, COOH). Found, %: C 72.00; H 6.40. $C_{13}H_{14}O_3$. Calculated, %: C 71.50; H 6.40.

Compound **Vb** (R^1 = CH_3, R^3 = H). Yield 80%, mp 147–148°C, R_f 0.68 (A). ^1H NMR spectrum, δ, ppm: 0.65 d and 1.15 d (3H, 2-CH_3, J = 7.0 Hz), 2.20–2.80 m (4H, CH_2CH_2), 3.14 q (1H, 2-H, J = 7.0 Hz), 7.25–7.50 m (5H, C_6H_5), 10.15 s (1H, COOH). Found, %: C 71.90; H 6.60. $C_{13}H_{14}O_3$. Calculated, %: C 71.50; H 6.40.

Compound **Vc** (R^1 = R^3 = CH_3). Yield 68%, mp 172–173°C, R_f 0.42 (B). ^1H NMR spectrum, δ, ppm: 0.60 d and 1.15 d (3H, 2-CH_3, J = 7.0 Hz), 1.05 d.d and 1.13 d.d (3H, 4-CH_3, J = 7.0 Hz), 2.05–3.00 m (3H, 5-H, 4-H), 3.24 q (1H, 2-H, J = 7.0 Hz), 7.35–7.50 m (5H, C_6H_5), 10.17 s (1H, COOH). Found, %: C 72.10; H 6.60. $C_{14}H_{16}O_3$. Calculated, %: C 72.40; H 6.90.

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