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LETTERS TO THE EDITOR

Acylation of Toluidines with 1,4-Dimethylcyclohex-3-enecarbonyl Chlorides

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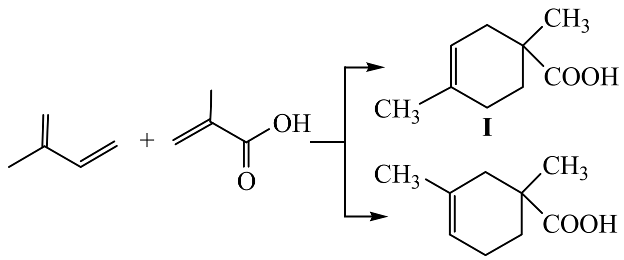
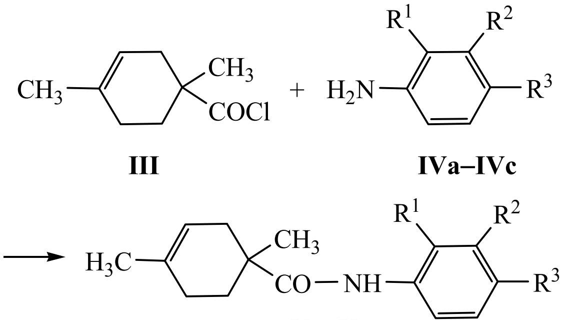
Amide group is a component of various compounds, which are of great practical importance. Organic compounds containing the amide groups in the molecule are obtained mainly by the acylation of amines with carboxylic acids and their derivatives. In the literature, there is enough information on the acylation of amines with aromatic carboxylic acids [1], their chlorides [2], esters [3], and anhydrides [4]. Among the acylating agents the carboxylic acid chlorides are the stronger electrophilic reagents. However, there are no published data on the acylation of amines with carboxylic acid chlorides of the cyclohex-3-ene series. We first investigated the acylation of amines with alicyclic carboxylic acid chlorides. Recently, the acylation of aromatic mono- and diamines as well as functionally substituted monoamines have been studied [5, 6]. Continuing research in this area, we studied the acylation of toluidine with cyclohex-3-enecarbonyl chloride **III**. 1,4-Dimethylcyclohexenecarboxylic acid **I** was synthesized by us via the Diels–Alder condensation of isoprene with methacrylic acid [7]. The isomers separation was performed by the method [8].



I

II

The 1,4-dimethylcyclohex-3-enecarboxylic acid chloride **III** was obtained by the reaction of the acid **I** with PCl_3. The reaction of the acid chloride **III** with toluidine proceeds as follows.



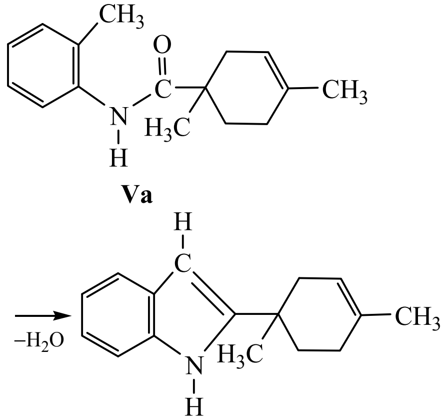
III

IVa–IVc

Va–Vc

$R^1 = CH_3$, $R^2 = R^3 = H$ (**a**); $R^1 = R^2 = H$, $R^2 = CH_3$ (**b**); $R^1 = R^2 = H$, $R^3 = CH_3$ (**c**).

In contrast to the *meta*- and *para*-toluidine, *o*-toluidine is a stronger nucleophilic substrate due to the positive inductive effect (+*I*) of the methyl group in the *ortho*-position with respect to the amine moiety. In this regard, in the reaction of the acid chloride **III** with *o*-toluidine **IVa** a part of the liberated HCl reacts with *o*-toluidine to form the corresponding ammonium salt. As a result, the target carboxamide compound **Va** is



Va

VI

obtained in a low yield. To prevent this disadvantage, the starting amine **IVa** was taken in excess. The yield of carboxamide **Va** increases to 90–93% as the reagents ratio **III**:**IVa** equals 1:1.3.

Increasing the reaction temperature also increases the yield of the desired product. Under the Madelung reaction conditions the carboxamide **Va** undergoes the intramolecular cyclization to form the corresponding indole **VI**.

The structure of the obtained compounds was confirmed by the IR and NMR spectroscopy.

1,4(1,3)-3-Dimethylcyclohex-3-enecarboxylic acids (III). A mixture of 258 g (3 mol) of methacrylic acid, 184 g (3 mol) of isoprene, and 200 ml of toluene was heated in the presence of 2 g of hydroquinone for 2 h in a rotating pressure reactor at a temperature of 180–200°C. After the usual treatment of the reaction mixture 452.64 g (92%) of the adduct was obtained as a mixture of isomers, which were separated by the known method [8] to afford 398.32 g (88%) of 1,4-dimethylcyclohex-3-enecarboxylic acid **I** (mp 62–63°C) and 54.3 g (12%) of 1,3-dimethylcyclohex-3-enecarboxylic acid **II** [mp 131.5–133°C (10 mm Hg), n_D^{20} 1.4741]. Physico-chemical constants of the obtained acids were identical to the published data [7].

1,4-Dimethyl-*N*-*o*-tolylcyclohex-3-enecarboxamide (IVa). A three-neck flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel was charged with 100 ml of *p*-xylene and 13.92 ml (0.13 mol) of *o*-toluidine. Then to a mixture was added 17.25 g (0.1 mol) of 1,4-dimethylcyclohex-3-enecarbonyl chloride **III** under stirring. The temperature of the reaction mixture rose to 55°C. After the addition of acid chloride **III** the reaction mixture was heated at 125–130°C for 5 h and left overnight. The crystals precipitated on cooling were filtered off and washed with water. Then the obtained crystals were recrystallized from aqueous ethanol. Yield 3.22 g (90.67%), mp 70–72°C, R_f 0.34. IR spectrum, ν, cm^{-1}: 3330 (N–H), 1670 (CO–NH), 1630 (C=C$_{\text{cycle}}$), 1600, 1520, 1480 (C=C$_{\text{Ar}}$), 760 (C=C$_{\text{Ar}}$). ^{1}H NMR spectrum, δ, ppm: 1.30 s (3H, CH_3), 1.70 s (3H, =CCH_3), 2.20 s (3H, Ar-CH_3), 1.90–2.10 m (4H, 2CH_2), 2.40–2.55 m (2H, CH_2), 5.40 s (1H, =CH), 7.10–7.25 m (4H, C_6H_4), 8.90 s (1H, NH).

1,4-Dimethyl-*N*-*m*-tolylcyclohex-3-enecarboxamide (IVb) was prepared similarly in a *p*-xylene medium (80 ml) from 8.60 g (0.05 mol) of 1,4-dimethylcyclohex-3-enecarbonyl chloride **III** and 5.35 g (0.05 mol) of *m*-toluidine. Yield 11.32 g (93.20%), mp 75–76°C (EtOH–H_2O), R_f 0.38. IR spectrum, ν, cm^{-1}: 3320 (N–H), 1675 (CO–NH), 1640 (C=C$_{\text{cycle}}$), 1580, 1500 (C=C$_{\text{Ar}}$), 870 (C=C$_{\text{Ar}}$).

1,4-Dimethyl-*N*-*p*-tolylcyclohex-3-enecarboxamide (IVc) was obtained similarly in a *p*-xylene medium (70 ml) from 11 g (0.064 mol) of the acid chloride **III** and 6.8 g (0.064 mol) of *p*-toluidine. Yield 14.38 g (92.50%), mp 95–97°C (EtOH–H_2O), R_f 0.38. IR spectrum, ν, cm^{-1}: 3320 (N–H), 1675 (CO–NH), 1640 (C=C$_{\text{cycle}}$), 1580, 1500 (C=C$_{\text{Ar}}$), 870 (C=C$_{\text{Ar}}$).

2-(1,4-Dimethylcyclohex-3-enyl)-1*H*-indole (V). A mixture of 24.3 g of carboxamide **IVa**, 6.07 g of sodium *n*-butoxide and 80 ml of *n*-butanol was placed into a three-neck flask equipped with a mechanical stirrer, a thermometer, and a reflux condenser with a trap. The reaction mixture was heated with stirring at a temperature of 135–140°C for 6 h and kept overnight. The precipitate was filtered off and washed several times with water. Yield 19.50 g (86.70%), mp 58–59°C, R_f 0.26. IR spectrum, ν, cm^{-1}: 3070 (N–H), 1635 (C=C$_{\text{cycle}}$), 1580, 1490 (C=C$_{\text{Ar}}$), 750 (C=C$_{\text{Ar}}$). ^{1}H NMR spectrum, δ, ppm: 1.25 s (3H, CH_3), 1.65 s (3H, = C–CH_3), 1.95–2.15 m (4H, 2CH_2), 2.50–2.60 m (2H, CH_2), 5.48 s (1H, =CH), 5.80 s (1H, =CH), 7.20–7.30 m (4H, C_6H_4), 9.5 s (1H, NH).

The IR spectra were recorded on a UR-20 instrument for suspensions in liquid paraffin. The ^{1}H NMR spectra were taken on a Bruker 300 spectrometer (300 MHz) from 5–15% solutions in CCl_4, internal reference HMDS. The TLC was performed on a silica gel eluting with a petroleum ether–diethyl ether–acetic acid system (90:10:4.5).

REFERENCES

1. Shteinberg, A.Ya., Kondratova, S.A., and Shein, S.I., *Zh. Org. Khim.*, 2005, vol. 41, no. 2, p. 312.
2. Bogatkov, S.V., Kruglikova, R.I., Lavrukhina, A.V., and Cherkasov, E.M., *Zh. Org. Khim.*, 1965, vol. 1, no. 5, p. 885.
3. Petyunin, P.A. and Choudri, A.M., *Khim. Geterotsikl. Soed.*, 1982, no. 5, p. 684.
4. Kas'yan, L.I., Tarabara, I.N., Pal'chikov, V.A., Krishchik, O.V., Isaev, A.K., and Kas'yan, A.O., *Zh. Org. Khim.*, 2005, vol. 41, no. 10, p. 1561.
5. Rustamov, M.A., Eivazova, Sh.M., and Nabiev, R.F., *Khim. Problemy*, 2005, no. 4, p. 101.
6. Rustamov, M.A. and Eivazova, Sh.M., *Poisk, Ser. Estestv. i Tekhn. Nauk*, 2009, no. 4, p. 10.
7. Nazarov, I.N., Titov, Yu.A., and Kuznetsova, A.I., *Izv. Akad. Nauk, Ser. Khim.*, 1959, no. 8, p. 1412.
8. Ismailov, A.G., Rustamov, M.A., and Akhmedov, A.A., USSR Author's Certificate no. 693680; C07C 51/42, C07C 57/04.