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An Efficient Synthesis of Medium-size Heterocycles Fused to Aryl Rings, Benzazepan, Benzazocan and Benzazonan-1-ones by Friedel-Crafts Acylation

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Since 7,8,9-membered heterocyclic compounds such as benzazepan, benzazocan and benzazonan-1-ones are important systems in medical and industrial technology, we tried to prepare such heterocycles through simple and effective reactions using amino acids as precursor.

Key Words: Medium-ring heterocycles, Friedel-crafts acylation, Intramolecular cyclization.

INTRODUCTION

Functionalized, heteroatom-containing rings are most important compounds in organic chemistry[1]. They found in several natural products[2] and simplified analogues as well as structural motifs resembling these natural products are interesting synthetic targets[3].

Synthetic routes to medium-ring heterocycles involving direct ring closure are often slow and hampered by unfavorable enthalpies (the strain in many medium rings) and entropies (probability of the chain ends meeting)[4]. Today, the most powerful methodology for the synthesis of medium-sized rings is the ring-closing metathesis (RCM) that sometimes requires high dilution conditions for successful conversion and often involves generation of byproducts such as ethylene[5-9]. As a part of our interest in the synthesis of medium-ring heterocycles, it is planned to synthesize benzofused seven, eight and nine-membered-ring compounds by using intramolecular Friedel-Crafts acylation.

Friedel-Crafts acylation is one of the most important protocols for bringing about the formation of carbon-carbon bonds between aromatic rings and aliphatic moieties[10,11]. In a typical Friedel-Crafts acylation reaction, an aromatic compound undergoes electrophilic substitution with an acylating agent in the presence of acid catalyst (*e.g.,* anhydrous $AlCl_3$)[12,13].

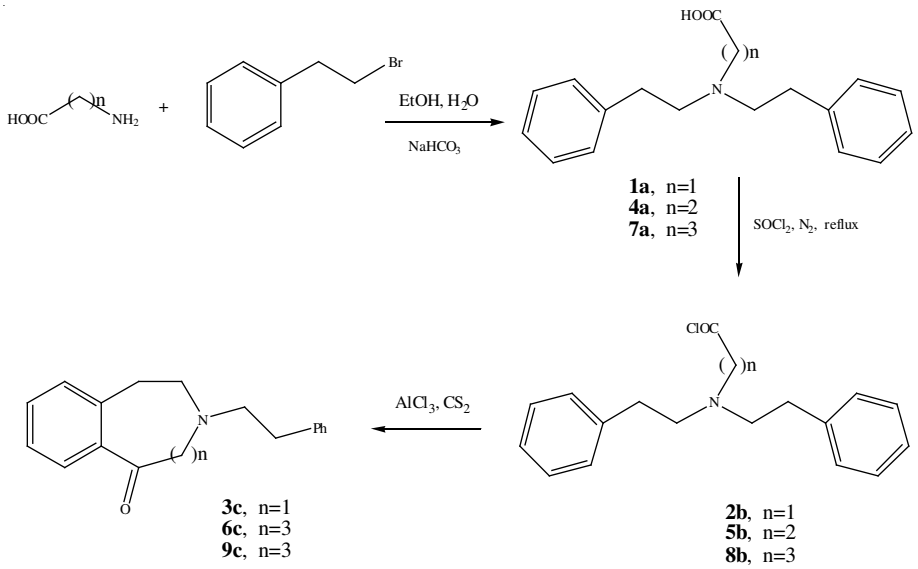
EXPERIMENTAL

All ^1H and ^{13}C NMR data were recorded on a Bruker Advanced DPX 400 MHz instrument spectrometer using Me_4Si as the internal standard in $CDCl_3$. IR spectra were recorded on a Bomem MB-Series 1998 FT-IR spectrometer. Chemicals were

purchased from Fluka, Merck and Aldrich chemical companies. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

General procedure

Synthesis of 1a: Place 2.48 g (0.033 mol) glycine, 5.55 g (0.066 mol) $NaHCO_3$, 15 mL water, 15 mL ethanol in a 250 mL round bottomed flask attached to a reflux condenser and mix for 5 min. Introduce 9 mL β-phenyl ethyl bromide and reflux the mixture on an oil bath at *ca*. 110 °C for 5 h. Allow the reaction mixture to cool to room temperature and placed in refrigerator for overnight. Then separate the solvent by rotary *in vacuo*. Further purification achieve by crystallization. 6 N HCl is added drop wise with stirring until pH = 6. The mixture stirred vigorously with 40 mL ether. The precipitate which is formed is then filtered and dried; the yield is 7.8 g (91 %). IR (neat, ν_{max}, cm^{-1}): 3400 1600 1461 1036 750. ^1H NMR (400 MHz, DMSO) δ 2.4 (s, 1H), 2.7 (t, 4H), 2.9 (t, 4H), 3.4 (d, 2H), 7-7.5 (m, 7H).



Structure of synthesis of benzazepan, benzazocan and benzazonan-1-ones

Synthesis of 2b and 3c: Place **1** (0.008 mol, 2.3 g), freshly distilled $SOCl_2$ (8 mL) in a 100 mL of 2-necked flask and heat under reflux (80 °C) for 40 min. The colour of the mixture changed from umber to dark brown. The unreacted thionyl chloride was distilled out. In order to synthesize **3**, place 10 mL of CS_2, $AlCl_3$ (1.07 g) to the flask and reflux the mixture for 2 h. After that, add piece of ice and drop wise HCl (6 N) until no gas produce. Extract the products with 50 mL of acetone. To separate **3c**, wash the organic layer with ether (5 × 50 mL), collect and evaporate the solvent *in vacuo* to give the product in 48 % isolate yields. Further purification achieved by TLC or by alumina neutral column chromatography and CH_2Cl_2, petroleum ether

solvents. IR (neat, ν_{max}, cm^{-1}): 3050 1670 1480 1260 750. ^1H NMR (400 MHz, DMSO) δ 1.3 (t, 2H), 1.5 (t, 2H), 2.5 (t, 2H), 3.5 (s, 2H), 4.0 (t, 2H), 7.1-7.6 (m, 9H).

Synthesis of 4a: Place and mix 2.5 g (0.033 mol) β-alanine, 5.55 g (0.066 mol) $NaHCO_3$, 15 mL ethanol and 15 mL water as same for **1**. Reflux the mixture for 6 h in 130 °C. Then allow to cool at 4 °C for 2 days and solvent remove by rotary evaporation, dilute the residue with 5 mL of water and made the solution slightly acidic (pH = 5-6). Add 180 mL (100 mL dioxane: 80 mL DMSO) with portions; filter off the white crystalline and wash with cold acetone. Dry the product in the oven at 60 °C; the yield is 8.9 g (90 %). IR (neat, ν_{max}, cm^{-1}): 3400 1400 1100 750 690. ^1H NMR (400 MHz, DMSO) δ 1.5 (t, 6H), 2.8 (t, 2H), 3.5 (m, 1H), 4.5 (t, 4H), 7.2 (s, 10H).

Synthesis of 5b, 6c, 8b and 9c: The procedure is the same as that described for **2b**. Reflux contiue to 40 min at 90 °C. Separate the residue thionyl chloride and introduce 10 mL of CS_2 and 1.07 g $AlCl_3$ to the flask and reflux the mixture for 2.5-3.0 h at 80 °C. Evaporate the solvent and add pieces of ice, a few drops of HCl (6 N) with mechanical stirring. Extract with 30 mL acetone, add decolourising charcoal, filter and concentrate to 20 mL of solution; the yield is 49 % (1.1 g). IR (neat, ν_{max}, cm^{-1}): 3015 1660 1420 1200 1080. ^1H NMR (400 MHz, DMSO) δ 2.3 (t, 2H), 2.5 (t, 2H), 2.6 (t, 2H), 3.1 (t,2H), 3.8 (t, 4H), 7.2 (m, 9H). Compound **9c** extract with 25 mL ether, dry with Na_2SO_4 and evaporete the solvent *in vacue*. The yield is 49 % (0.86 g). IR (neat, ν_{max}, cm^{-1}): 3015 17131420 1200 1100. ^1H NMR (400 MHz, DMSO) δ 1.1 (m, 2H), 1.3 (t, 2H), 2.2 (t, 2H), 2.5 (t, 2H), 2.8 (t, 4H), 3.1 (t, 4H), 7.1 (m, 10H).

RESULTS AND DISCUSSION

Present synthesis started from the acid derivatives of diphenyl ethyl amine (entry **1a**, **4a**, **7a**). One of the most important things into design this synthetic strategy, to find a convenient solvent, due to different properties of the reactants. The amino acids that be used are salt form and soluble in water. Thus, we used a mixture of water and ethanol 1:1. The products, amino acids, extracted and purified using isoelectric point.

The reaction of β-phenylethyl bromide with amino acids (glycine, β-alanine and γ-butanoic acid) gave the condensed products **1a**, **4a** and **7a** in good yields. Then acid functional groups of amino acids were converted to carbonyl chloride with thionyl chloride, the unreacted thionyl chloride was distilled out. The yields of reaction for proceeding of the next processes are quality appropriate and separating and purifying of products are simple (entry **2b**, **5b**, **8b**). Then, intra-molecular ring-closings were carried out in presence of CS_2 solvent by addition of $AlCl_3$ as a catalyst. The cyclized products would be obtain in good to moderate yields (entry **3c**, **6c**, **9c**).

Conclusion

In conclusion, the most remarkable feature of this reaction is that the synthesis of 7-, 8- and 9-membered ring can be simply realized by variation of the length of carbon chain of the starting material. The methodology developed may prove to be helpful for the preparation of other derivatives of similar complexity.

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