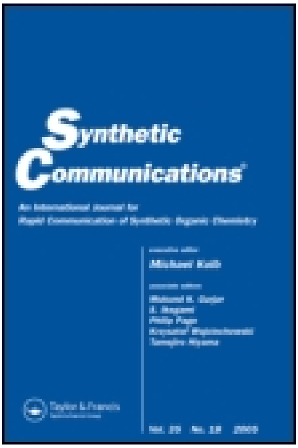

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A Novel Synthesis of Bisbenzyl Ketones by DCC Induced Condensation of Phenylacetic Acid

Sumita Bhandari [a] & Suprabhat Ray [a]
[a] Medicinal Chemistry Division, Central Drug Research Institute, Lucknow, 226001, India

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A NOVEL SYNTHESIS OF BISBENZYL KETONES BY DCC INDUCED CONDENSATION OF PHENYLACETIC ACID

Sumita Bhandari and Suprabhat Ray*

Medicinal Chemistry Division, Central Drug Research Institute,
Lucknow-226001, India

Abstract: 1,3-Dicyclohexylcarbodiimide (DCC) has been found to effect condensation of two molecules of phenylacetic acids in the presence of dimethylaminopyridine leading to the formation of bisbenzyl ketones.

1,3-Dicyclohexylcarbodiimide (DCC) is a powerful dehydrating agent, generally used for the preparation of amides, anhydrides, esters etc[1,2] . The reaction is usually carried out in an aprotic solvent at low temperatures. It is a very common reagent for the preparation of peptides[3]. In the preparation of esters, the presence of an acylation catalyst, such as 4-dimethylaminopyridine (DMAP) is required[2].

In a study of DCC induced preparation of amides by condensation of 4-methoxyphenylacetic acid with 4- acetoxyaniline in dichloromethane, it was observed that when the reaction was conducted at room temperature (25-30^{0}C) instead

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*To whom correspondence should be addressed

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of 0-4^{0}C reported for the preparation of the amide bond, in the presence of DMAP as a catalyst, the product obtained did not show incorporation of the amine moiety. IR spectrum showed a peak at 1725 cm^{-1} instead of the amide peak at 1650 cm^{-1} and the phenolic acetate peak at 1755 cm $^{-1}$ was also absent .^{1}HNMR of the above compound showed aromatic protons as two doublets of an AA`BB` system at 6.84 and 7.1δ .The mass spectrum of the compound showed molecular ion peak at 270.

On the basis of the above spectral data and elemental analysis, the product was identified as bis- 4-methoxy benzyl ketone (**1**).

When the above reaction was conducted without addition of the aniline derivative, formation of bisbenzyl ketone was observed in about 60% yield.Unreacted phenylacetic acid mainly accounted for the rest of the material. In the absence of DMAP, the reaction failed to proceed.

Preparation of the bisbenzyl ketones has been reported earlier through treatment of phenylacetic acid with NH_3 and subsequent distillation of its Pb salt[4].To the best of our knowledge,formation of a bisbenzylic ketone in a DCC induced condensation reaction has been observed for the first time.

In order to study the generality of the reaction and its mechanism, differently substituted phenylacetic acids were used. Characterisation data of bisbenzyl ketones thus prepared is given in the Table.

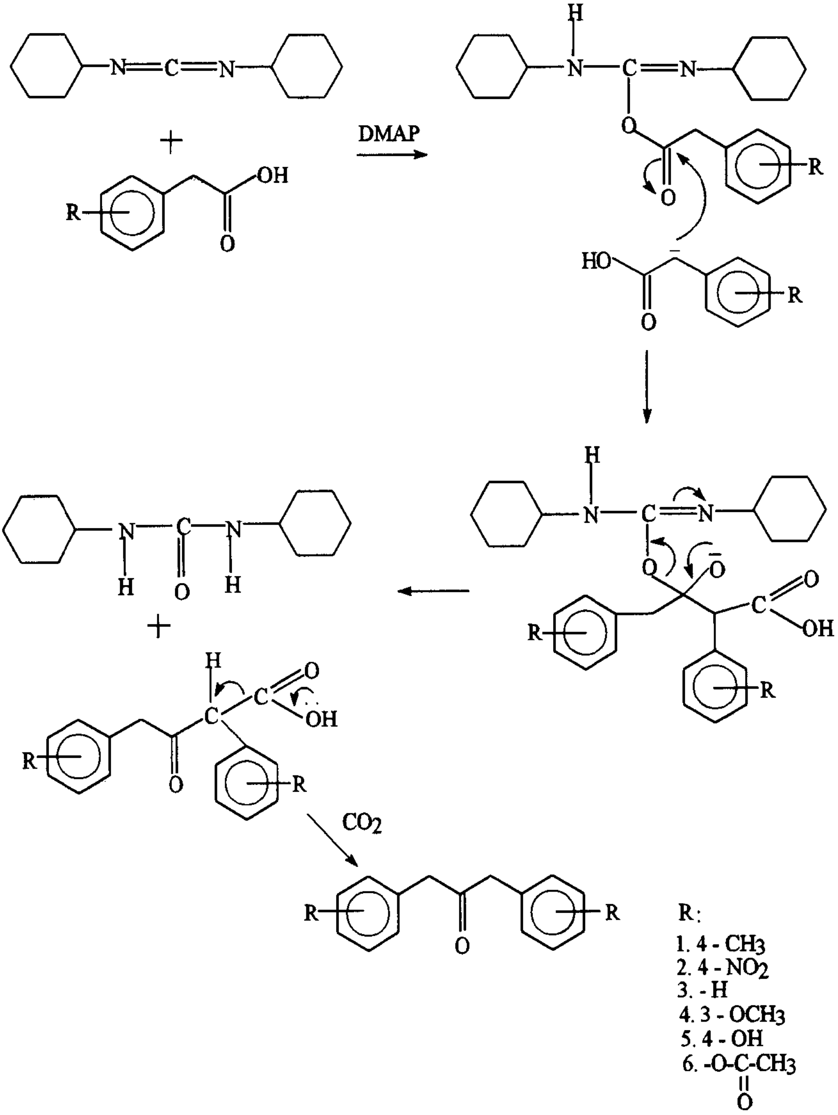
A likely course of the reaction mechanism would involve self condensation of two molecules of the phenylacetic acid in which the active methylene (benzylic methylene) of one would attach to the carbonyl group of another followed by decarboxylation. Therefore, nucleophilicity of the benzylic group is expected to play

Table: Data of bisbenzyl ketones prepared

Comp No.	M.p. ^{0}C	Yield %	Mass m/e	^{1}HNMR(ppm) (δ,CDCl$_3$)	IR (KBr,c.m^{-1})
1.	86	68	270	7.1 (d,4H,- Ar) 6.84(d,4H,-Ar) 3.8 (s,6H-,OCH$_3$) 3.64(s,4H,-2CH$_2$)	2930(-CH$_2$) 1725(-C=O) 1600(-Ar) 1240(-OCH$_3$)
2.	214	49	300	8.2(d,4H,-Ar) 7.33(d,4H,-Ar) 3.9(s,4H,-2CH$_2$)	2930(-CH$_2$) 1722(-C=O) 1600(-Ar) 1514(-NO$_2$) 856.3(-ArNO$_2$)
3.	Oil	64	210	7.2(m,10H,-Ar) 3.6(s,4H,-2CH$_2$)	2930(-CH$_2$) 1700(-C=O) 1600(-Ar)
4.	60	68	270	7.08(d,4H,-Ar) , 6.88 (d,4H,-Ar) , 3.8(s,6H,-OCH$_3$) 3.6(s,4H,-2CH$_2$).	2929(-CH$_2$) 1720(-C=O) 1600(-Ar) 1240(-OCH$_3$)
5.	164	34	242	6.94(d,4H,Ar), 6.8(d,4H,-Ar) , 3.6(s,4H,2CH$_2$), 8.7(s,1H,-OH)	3400(-OH) 2930(-CH$_2$) 1724(-C=O) 1600(-Ar)
6.	100	70	326	7.19(d,4H,-Ar), 7.06(d,4H,-Ar), 3.8(s,4H,-2CH$_2$), 2.38(s,6H,-2CH$_2$)	2930(-CH$_2$) 1790(-OAc) 1725(-C=O) 1600(-Ar)

a crucial role. Accordingly, when the electron donating 4-methoxy group was removed or replaced by an electron withdrawing 4-NO$_2$, formation of the bisbenzyl ketone was observed in poor yield. Since anhydride formation is known to occur in a DCC catalysed reaction, it was thought that an anhydride intermediate is participating in the

Scheme : Mechanism of formation of bisbenzyl ketones



condensation with another molecule of the acid . Such an intermediate would undergo facile decarboxylation. However, when anhydride of phenylacetic acid prepared from corresponding acid chloride following a known procedure[5] was taken into CH_2Cl_2 and treated with DMAP at room temperature in the usual manner, it did not lead to the formation of bisbenzyl ketone.

Failure of the reaction in the absence of DMAP suggests the role of this acylation catalyst and hence an intermediate ester formation.On the basis of the parameters mentioned above, the following reaction mechanism shown in the Scheme has been suggested.

Experimental Section :

^1H NMR (in $CDCl_3$) were recorded on a WM-400(400MHZ) NMR spectrometer using TMS as internal reference(chemical shift in δ ppm).FTIR spectra were taken in KBr or neat on 8201 PCShimadzu spectrometer.Mass spectra were recorded on a Jeol JMSD-300 mass spectrophotometer.Microanalysis were done on Carlo ebra model EA-11108 and HeraeusCHN rapid instrument.Melting point apparatus type 9EC45A.

General procedure for the synthesis of bisbenzyl ketones (1-4)

A solution of substituted phenylacetic acid (1mol) in dry dichloromethane was added slowly to a solution of DCC (1mol) and DMAP (1/4mol) in dry dichloromethane . Reaction mixture was kept for 24 hrs. at room temperature and then filtered. The filtrate was distilled off and the residue was chromatographed over silica gel using increasing amounts of ethyl acetate in benzene as eluant when the desired compound eluted first. The compound was recrystallized from methanol-hexane.

Synthesis of bis(4-hydroxybenzyl) ketone

Pyridinium chloride and bis(4-methoxybenzyl) ketone were heated at 200°C for 15 min. The reaction mixture was then poured on to ice cold water and extracted with ethyl acetate. The compound was chromatographed over silica gel using hexane-ethyl acetate as eluant. The compound obtained was recrystallized from methanol-hexane.

Synthesis of bis(4- acetoxybenzyl) ketone

Acetic anhydride (2 mol) was added to a solution of bis(4-hydroxybenzyl) ketone (1 mol) in dry pyridine and the reaction was left overnight at room temperature. The reaction mixture was then poured on to water, acidified with dil HCl solution, extracted with solvent ether, washed with water and dried over Na_2SO_4. Ether solution was then concentrated to give the desired product which was recrystallized from pentane.

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References & Notes :

1. Fieser, L.F; Fieser, M; " Reagents for Organic Synthesis "A Wiley interscience Publication, John Wiley & Sons, **1980**, *8*, pp.162-163.

2. "Encyclopedia of Reagents for organic Synthesis" Editor in Chief, Paquette,L.A, **1995**, *3*, 1751-1753.

3. Sheehan, J.C; Hess, G.P; *J.Am.Chem.Soc.*, **1955**, *77*, 1067

4. Chiavarelli, S; Settimj,G; Alves,H.M; *Gazz. Chim. ital.*, **1957**, *87*, 109-19. *Chem.*

*Abstr.*52:15519f.

5. Cohen, T; Fager, J.H; *J.Am.Chem.Soc.*, **1965**, *87*, 5701

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