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Synthesis of 1,3-Disubstituted Hexahydropyrimidine Derivatives from Dibenzoylmethane, Acetylacetone, Ethyl Acetoacetate: One-Pot FeCl_3 -Catalyzed Mannich Reaction

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SYNTHESIS OF 1,3-DISUBSTITUTED HEXAHYDROPYRIMIDINE DERIVATIVES FROM DIBENZOYLMETHANE, ACETYLACETONE, ETHYL ACETOACETATE: ONE-POT FeCl₃-CATALYZED MANNICH REACTION

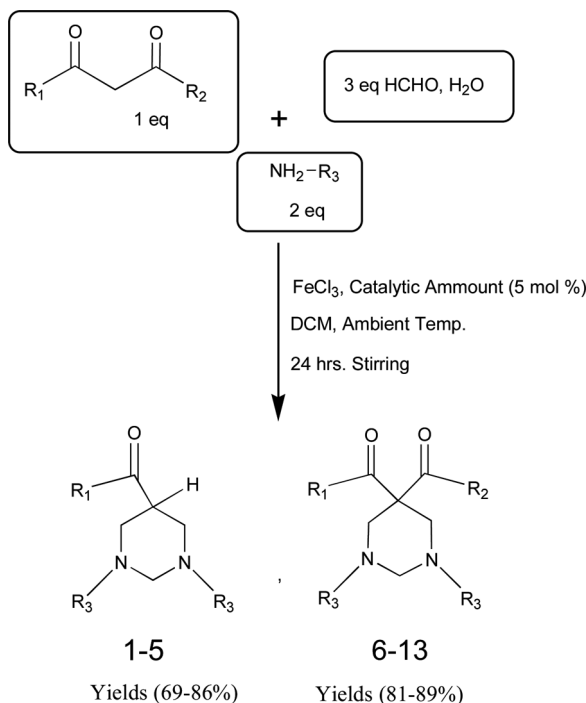
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GRAPHICAL ABSTRACT



Abstract 1,3-Disubstituted hexahydropyrimidin-5-yl(phenyl)methanone (products **1–5**) were prepared from the reaction of dibenzoylmethane with primary amines and formaldehyde in the presence of Lewis acid catalyst at ambient temperature. Replication of the

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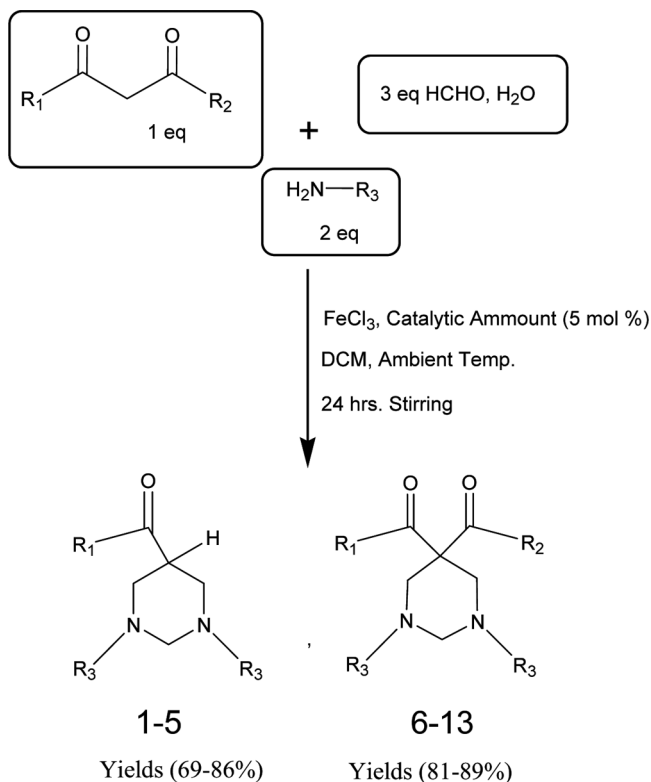
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reaction with acetylacetone and ethyl acetoacetate yielded 1,1'-(1,3-disubstituted hexahydropyrimidine-5,5-diyl)diethanone (products **6–10**) and ethyl 5-acetylhexahydropyrimidine-5-carboxylate (products **11–13**), respectively. Yields obtained ranged from 69 to 89%.

Keywords Debenzoylation; hexahydropyrimidines; Mannich reaction

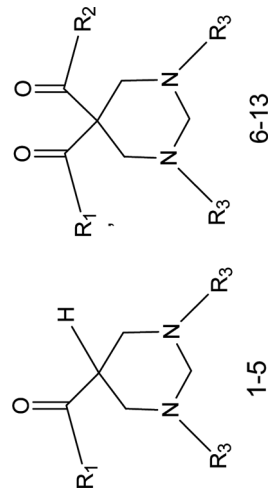
INTRODUCTION

Hexahydropyrimidines are compounds with broad biological activities and have been found in many natural products.^[1–5] A number of these compounds are suspected to have important biological activities.^[6–16] Recent in vitro testing of some hexahydropyrimidine derivatives showed promising new leads with pharmaceutical interest. Biological activities include, for example, leishmanicidal,^[17] antimicrobial,^[7] and cytotoxic activities.^[18] Several hexahydropyrimidine derivatives also have been evaluated for their anti-HIV-1 activity.^[19,20] Anti-inflammatory and analgesic activities of some hexahydropyrimidines were evaluated with comparable results to diclofenac sodium gel (Relaxyl gel) and aspirin.^[21,22] Additionally, hexahydropyrimidines were important as transport molecules for tumor inhibition and antineoplastic



Scheme 1. Synthesis of hexahydropyrimidines using dibenzoylmethane, primary amine, and formaldehyde.

Table 1. Yields and structures of products obtained according to Scheme 1



Parameter	Entry												
	1	2	3	4	5	6	7	8	9	10	11	12	13
R ₁	Ph	Ph	Ph	Ph	Ph	Me	Me	Me	Me	Me	Me	Me	Me
R ₂	—	—	—	—	—	Me	Me	Me	Me	Me	OEt	OEt	OEt
R ₃	p-Cl-Ph	cyclohexyl	p-Br-Ph	n-Hexyl	p-OMe-Ph	p-Cl-Ph	Cyclohexyl	p-Br-Ph	Ph	p-OMe-Ph	p-Cl-Ph	Cyclohexyl	p-Br-Ph
Yield (%)	77	71	89	69	86	86	85	83	87	89	81	84	85

activity.^[15,23–27] Antiviral activity of hexahydropyrimidines were also tested with interesting results.^[28]

Acid-mediated aminomethylation with formaldehyde and primary amines at the α -position of 1,3-dicarbonyl compounds is a well-established procedure for the synthesis of hexahydropyrimidines.^[29–34] Indeed several 1,3-dicarbonyl compounds have been reported to undergo this reaction under mild conditions at room temperature in the presence of catalytic amounts of FeCl_3 .^[35] However, reports of this reaction with dibenzoylmethane (DBM) are lacking. In an effort to prepare hexahydropyrimidine derivatives of DBM, the known one-pot procedure for related systems using FeCl_3 was initially pursued.^[35] Unexpectedly, when the products were isolated and identified, the monocarbonyl derivatives were obtained (Scheme 1, **1–5**). The expected dicarbonyl derivatives were not detected. It was evident that one of the benzoyl groups had been cleaved off in the course of the reaction. The presence of benzoic acid, a logical by-product of the debenzoylation, was confirmed by NMR, further supporting that conclusion. When DBM was replaced by either acetylacetone (ACAC) or ethyl acetoacetate (EAA), the expected dicarbonyl products were successfully isolated and characterized (Scheme 1, Table 1), suggesting that this observation is unique to the dibenzoyl system.

RESULTS AND DISCUSSION

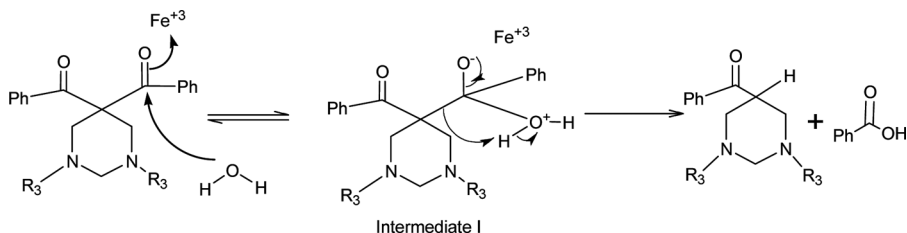
Primary amine (Table 1) was reacted with DBM in the presence of aqueous formaldehyde and a catalytic amount of FeCl_3 (5 mol%) in dichloromethane at room temperature (Scheme 1). The reaction was monitored by thin-layer chromatography (TLC). The product obtained was thoroughly purified and characterized by standard spectroscopic and analytical methods to show that one of the benzoyl groups had been cleaved off from the starting material dibenzoylmethane. Products obtained (**1–5**) are listed in Table 1.

To explore this observation further, the reaction was replicated with the same set of primary amines using acetylacetone and ethyl acetoacetate. In both cases, analogous deacylation was not detected. Furthermore, because literature procedure calls for only 6 h of stirring time, herein the elongated stirring time did not change the course of the reaction and the expected products (**6–13**) were obtained in comparable yields.^[35]

The reaction of ACAC, according to Scheme 1, was repeated at elevated temperature (refluxing temperature of chloroform). It was found that higher temperature did not affect the outcome of this reaction. In conclusion, all of the evidence, taken together, makes it apparent that the observed carbonyl group fission can be associated to the DBM system.

It turns out that the observed carbonyl group cleavage is not entirely unusual. There are several literature precedents in which deacylation and debenzoylation have been observed for 1,3-dicarbonyl compounds.^[37,38] An interesting debenzoylation have been observed for α,α -dialkylated dibenzoylmethane derivative when treated with alkali.^[39] However, the mechanism is still largely speculative.

The generally accepted mechanism for the reaction shown in Scheme 1 has been recently discussed by Mukhopadhyay et al.^[35] With this mechanism in mind, currently it is not clear at which step the benzoyl group is lost. In an effort to



Scheme 2. Debenzoylation of DBM-derived hexahydropyrimidines in the presence of FeCl_3 and water.

determine when the debenzylation was occurring, DBM was mixed with FeCl_3 alone under the reaction conditions. When the product mixture was analyzed by TLC, the formation of acetophenone, a putative by-product of the debenzylation should DBM denbzoylate in this case, was not detected. Similarly, benzoic acid did not form either. It is highly likely that both water (from the aqueous formaldehyde) and the Lewis acid catalyst, FeCl_3 , are playing a role. The formation of stoichiometric quantities of benzoic acid equivalent to that of the main product suggests that water is essential. The presence of Lewis acid catalyst ought to facilitate the nucleophilic addition of water to the carbonyl group. However, why this appears to only occur in the DBM case remains unclear. Additionally, the Lewis acid iron(III) chloride catalyst form is not known at this stage. A hydrated form ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) of the catalyst in the presence of water cannot be ruled out.

It is possible that the electron-withdrawing nature of the benzene ring just sufficiently activate the carbonyl carbon. If this were the case, systems with an electron-donating group attached to the benzene ring, or a mixed system containing only one benzoyl group may result in different reactions. Unfortunately, the former, to our knowledge, is not commercially available.

The observed debezoylation with DBM-hexahydropyrimidines is probably due to the FeCl_3 -assisted water nucleophilic addition to one of the carbonyl carbons of the initial hexahydropyrimidine product (Scheme 2). A transient intermediate **I** will be a logical product of this addition. The adjacent phenyl group will also play an assistive role in this nucleophilic addition. When DBM is compared to EAA and ACAC, the absence of this additional assistance might explain the survival of the dicarbonyl hexahydropyrimidine products of EAA and ACAC. Subsequently, the decomposition of intermediate **I** will ultimately lead to the observed cleavage of the carbon-carbon bond. The isolation of benzoic acid by-product supports that conclusion.

Literature procedures of DBM hexahydropyrimidine synthesis^[36] require heating at much greater temperatures and less commercially available starting materials. The present methodology has the advantages of taking place at room temperature using simpler starting material and with comparable yields although with lower overall atom economy.

EXPERIMENTAL

Column chromatography was performed on 230- to 400-mesh silica gel (Merck) and TLC plates with silica gel 60 F_{254} (Merck) were used. A mixture of

AcOEt/hexane (30%) was used as eluent for all chromatographic separations. Infrared (IR) spectra were recorded as either thin films or KBr discs on Magna-IR 560 Nicolet FT-IR spectrometer and are reported in wave numbers (cm^{-1}). NMR spectra were recorded at room temperature on Bruker-Avance (III) spectrometer at 400 MHz using CDCl_3 as solvent. Chemical shifts are expressed in δ values (ppm) relative to tetramethylsilane (TMS) as internal standard for ^1H and relative to TMS (0.00 ppm) or to CDCl_3 (77.05 ppm) for ^{13}C NMR spectra. Coupling constants J values are reported in hertz (Hz). Elemental analyses were performed on a EuroEA 3000, EuroVector CHN analyzer. Structural assignments of the derived compounds were established by analysis of their combined spectroscopic data.

General Procedure

A typical experimental procedure followed for the preparation of hexahydropyrimidines using either dibenzoyl methane, acetylacetone, or ethyl acetoacetate using FeCl_3 catalyst is as follows: A mixture of 1,3-dicarbonyl compound (1 equivalent), primary amine (2 equivalents), formaldehyde (3 equivalents, 37–41% aqueous solution), and a catalytic amount of FeCl_3 (5 mol%) was stirred for 24 h at room temperature in dichloromethane. The solvent was removed by a rotary evaporator. Crude products were purified by column chromatography with 30% ethyl acetate in hexane. Spectral and analytical data of all the compounds in Table 1 are given in the supplementary material. The spectral and analytical data of representative compounds are as follows.

Compound 1, [1,3-Bis(4-chlorophenyl)hexahydropyrimidin-5-yl](phenyl)methanone

White solid, FT-IR: ν_{max} (thin film)/ cm^{-1} 3052, 2827, 1674, and 1594; ^1H NMR (400 MHz,) δ_{H} : 7.93 (2H, d, $J=7.4$ Hz, PhH), 7.63 (1H, t, $J=7.4$ Hz, PhH), 7.51 (2H, t, $J=7.4$ Hz, PhH), 7.29 (4H, d, $J=8.7$ Hz, ArH), 7.01 (4H, d, $J=8.7$ Hz, ArH), 5.13 (1H, d, $J=11.3$ Hz, N-CH-N), 4.17 (1H, d, $J=11.3$ Hz, N-CH-N), 3.93–4.03 (3H, m, CH, CH), 3.34 (2H, t, $J=10.8$ Hz, CH); ^{13}C NMR (CDCl_3) δ_{C} : 199.4 (C, CO), 147.7 (C, C_{aromat}), 135.7 (C, C_{aromat}), 133.8 (CH, C_{aromat}), 129.4 (CH, C_{aromat}), 129.0 (CH, C_{aromat}), 128.2 (CH, C_{aromat}), 125.9 (C, C_{aromat}), 118.8 (CH, C_{aromat}), 68.7 (CH_2 , N- CH_2 -N), 52.4 (CH_2 , N- CH_2), 40.6 (CH, CO-CH). Anal. calcd. for $\text{C}_{23}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}$: C, 67.16; H, 4.90; N, 6.81. Found: C, 67.41; H, 4.92; N, 6.79.

Compound 6, 1,1'-[1,3-Bis(4-chlorophenyl)hexahydropyrimidine-5,5-diyl]diethanone

White solid, FT-IR: ν_{max} (thin film)/ cm^{-1} 3088, 2992, 1691, and 1583; ^1H NMR (400 MHz,) δ_{H} : 7.27 (4H, d, $J=8.8$ Hz, ArH), 7.01 (4H, d, $J=8.8$ Hz, ArH), 4.33 (2H, s, N- CH_2 -N), 3.81 (4H, s, CH_2 -N), 2.17 (6H, s CH_3); ^{13}C NMR (CDCl_3) δ_{C} : 203.2 (C, CO), 147.7 (C, C_{aromat}), 129.3 (CH, C_{aromat}), 126.6 (C, C_{aromat}), 119.2 (CH, C_{aromat}), 69.2 (CH_2 , N- CH_2 -N), 67.1 (C, C-CO), 53.3 (CH_2 , N- CH_2),

26.6 (CH₃). Anal. calcd. for C₂₀H₂₀Cl₂N₂O₂: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.67; H, 5.17; N, 7.13.

Compound 11, Ethyl 5-Acetyl-1,3-bis(4-chlorophenyl)hexahydropyrimidine-5-carboxylate

White solid, FT-IR: ν_{\max} (thin film)/cm⁻¹ 3065, 2983, 1771, 1593, and 1496; ¹H NMR (400 MHz, δ_{H} : 7.19 (4H, d, J = 8.9 Hz, ArH), 6.94 (4H, d, J = 8.9 Hz, ArH), 4.40 (1H, d, J = 11.5 Hz, N-CH-N), 4.32 (1H, d, J = 11.5 Hz, N-CH-N), 3.98 (2H, q, J = 7.1, CH₂-O), 3.90 (2H, d, J = 12.7 Hz, CH₂-N), 3.71 (2H, d, J = 12.7 Hz, CH₂-N), 2.18 (3H, s, CH₃-CO), 1.11 (3H, s, CH₃); ¹³C NMR (CDCl₃) δ_{C} : 202.0 (C, CO), 168.0 (C, COO), 147.8 (C, C_{aromat}), 129.1 (CH, C_{aromat}), 125.8 (C, C_{aromat}), 119.0 (CH, C_{aromat}), 67.4 (CH₂, N-CH₂-N), 61.9 (CH₂, CH₂-CO), 59.9 (C, CH₂-C-CH₂), 53.5 (CH₂, CH₂-N), 26.5 (CH₃, CH₃-CO), 13.8 (CH₃). Anal. calcd. for C₂₁H₂₂Cl₂N₂O₃: C, 59.87; H, 5.26; N, 6.65. Found: C, 60.03; H, 5.28; N, 6.68.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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