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On the mechanism of reaction between ketones and nitriles. Unexpected results from benzyl nitriles

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Abstract—Benzyl nitriles bearing electron donating groups react with ketones in the presence of trifluoromethanesulfonic anhydride to form naphthalene amines and related compounds. In contrast, the same benzyl nitriles substituted with electron withdrawing groups form the corresponding 2,4-dibenzyl substituted pyrimidines. A mechanism is proposed that explains the divergence in reaction paths leading to these products. © 2002 Elsevier Science Ltd. All rights reserved.

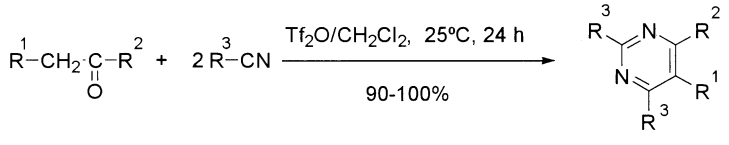
1. Introduction

Pyrimidines are prominent heterocyclic compounds because of their biological and pharmaceutical activity.[1,2] Among these, benzyl pyrimidines, are particularly versatile. For example, benzyl pyrimidines with 4-hydroxyl groups bind specifically to human serum albumin determining the drug distribution and its pharmacological effect on the organism.[3] Moreover, 2,6-disubstituted benzylpyrimidines have been found to be specific inhibitors of HIV-1 reverse transcriptase showing great effects and selectivity indexes.[4] The 4-(4-substituted)benzylpyrimidines are route-specific by-products in the Leuckardt preparation of amphetamine and its derivatives.[5] In addition, 5-(susbstituted benzyl)-pyrimidines present high activity against bacterial and avian dihydrofolate reductase.[6] Several methods for preparing benzyl pyrimidines are described in literature.[1] Most of these preparative methods require several step sequences to form the pyrimidine nucleus. In particular, benzyl pyrimidines can be prepared by dehalogenation of halogenobenzyl pyrimidines or by interconversion of different alkyl groups from alkyl pyrimidines. In spite of their importance, little is reported about the one step preparation of benzyl pyrimidines.[1]

The cyclization of ketones with nitriles in the presence of triflic anhydride, Tf_2O, ($(CF_3SO_2)_2O$) has been shown to be a very useful method for the preparation of alkyl and aryl pyrimidines.[7] This reaction affords pyrimidines **3** in good yields from ketones **1** and nitriles **2** (Scheme 1).

Application of this reaction to α-haloketones provided a route to 5-halopyrimidines,[8] while the reaction of aliphatic esters with nitriles leads to 4-alkoxypyrimidines.[9] More detailed applications of this reaction are found in Ref. 10.

On the other hand, naphthalene amines are also compounds of great interest. Among the several applications of these compounds, it is reported that 1-naphthlyamine derivatives are used as sensitizer for photoinitiated radical polymerization[11] and for the synthesis of novel conducting polymer.[12] Additionally 2-naphthlyamine derivatives are used as fluorescent post-column chelating agents,[13] and the carcinogenic effects of naphthalene amines are object of active



1 **2** **3**

Scheme 1.

Keywords: benzyl nitriles; naphthalene amines; benzyl pyrimidines; triflic anhydride.
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research.[14] Primary aromatic amines can be prepared by amination of aromatic compounds with hydrazoic acid[15] or with trimethylsilyl azide.[16] Other synthetic methods are based in the reaction of activated aryl halides with ammonia or amines.[17] The well-known Bucherer reaction involves the treatment of naphthols with ammonia and sodium bisulfite.[17] All of these synthetic procedures are based in chemical transformations on a preformed aromatic ring.

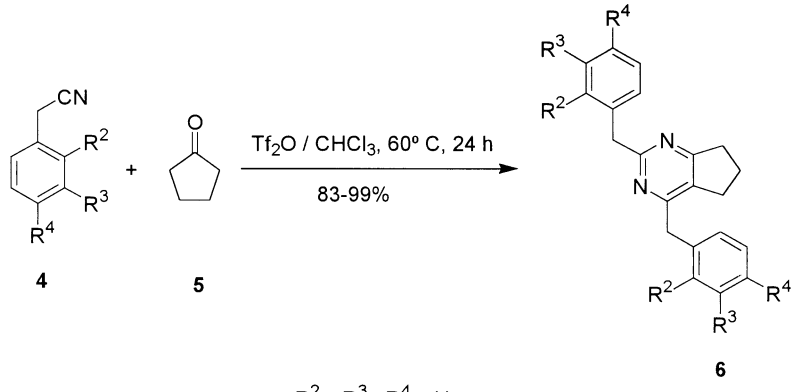
We will report here the reaction of aliphatic ketones with a variety of ring substituted benzyl nitriles in the presence of triflic anhydride. The nature of the product depends on the electronic character of the substituents attached to the aromatic ring of the benzyl nitrile. While electron withdrawing groups lead to the formation of benzyl pyrimidines in good yields, electron donating groups lead to substituted naphthalene amines. In this work, various experiments were carried out to isolate or identify intermediates that clarify the paths of these reactions. Based on these experiments, a mechanism is proposed that explains the formation of these diverse products.

2. Results and discussion

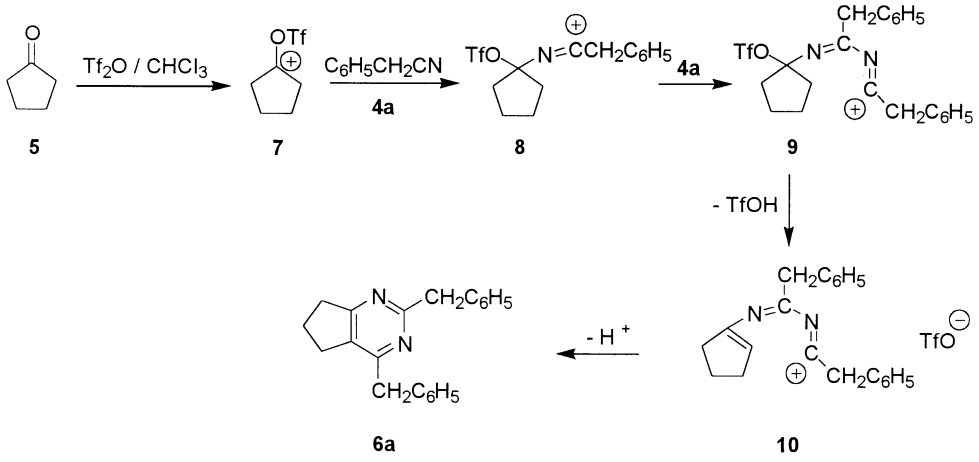
The 2,4-dibenzylpyrimidines **6a–e** were prepared in good yields following the general procedure[7] from the cyclization of ketones with nitriles in the presence of triflic anhydride (Scheme 2).

The mechanism proposed involves the formation of a trifliloxycarbenium ion (**7**) which is trapped by the nitrile **4a** forming a nitrilium ion (**8**). A second molecule of nitrile reacts with the intermediate to give the corresponding pyrimidine **6a**, after elimination of TfOH, cyclization and loss of a proton (Scheme 3).

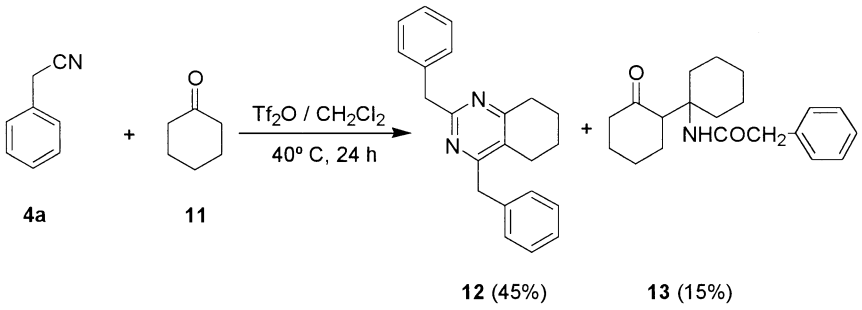
All the experiments were carried out on cyclopentanone **5** to avoid side reactions arising from the solvolysis of the vinyl triflate formed by reaction of Tf_2O and the ketone.[18,19] In this regard, it is well known that the cyclopenten-1-yl triflate does not solvolyze via a cyclopentenylcation; it reacts only under strong basic conditions through a O–S bond fission.[20–22] It is important to note that when the reaction was carried out with cyclohexanone **11**, the corresponding



Scheme 2.



Scheme 3.

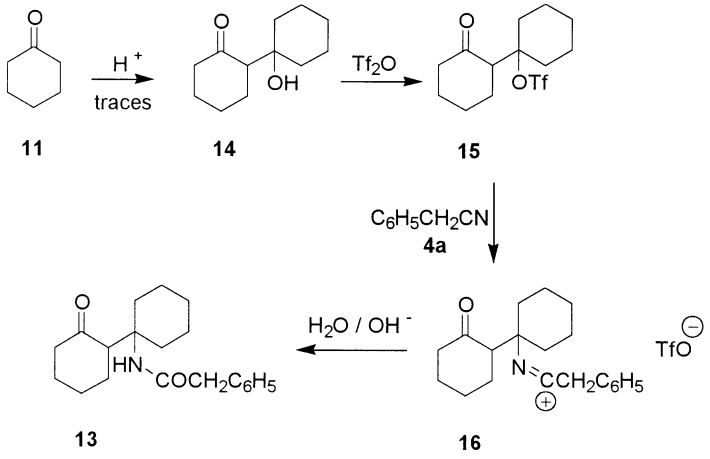


Scheme 4.

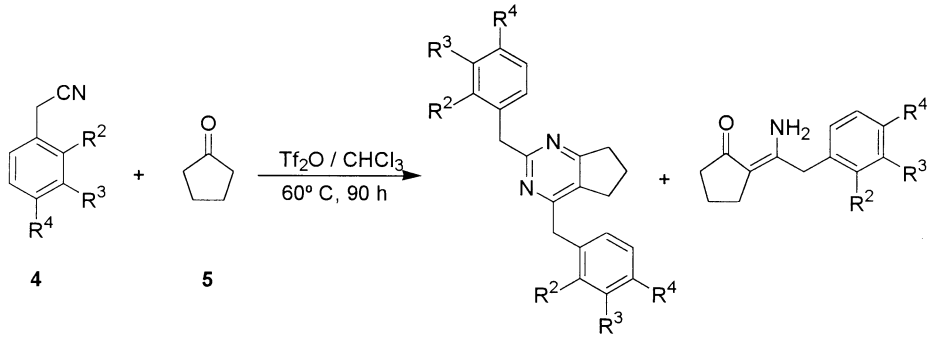
pyrimidine **12** was isolated in low yield due to the competitive formation of the amide **13** (Scheme 4).

The formation of this amide can be explained with a dimer (**14**) resulting from an aldol condensation of the ketone. Reaction of the dimer (**14**) with Tf_2O affords the triflate (**15**) which undergoes nucleophilic substitution by a nitrile molecule leading to the nitrilium salt (**16**). After basic hydrolysis and isomerization the corresponding amide (**13**) was isolated (Scheme 5). Similar results were also observed in the reaction of cyclobutanone with aliphatic and aromatic nitriles.[23]

The formation of amides from cyclobutanone and cyclohexanone (but not from cyclopentanone) can be explained by the different degrees of enol formation of these cycloalkanones. Thus, the amounts of enol present in cyclopentanone and cyclohexanone are 0.55 and 1.18%,



Scheme 5.



f; $R^2 = CH_3$; $R^3 = R^4 = H$
g; $R^2 = R^3 = H$; $R^4 = CH_3$
h; $R^2 = OCH_3$; $R^3 = R^4 = H$
i; $R^2 = R^3 = H$; $R^4 = OCH_3$

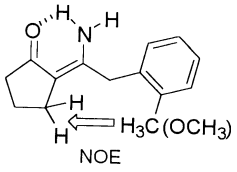
6f (74%) **17f** (18%)
6g (71%) **17g** (14%)
6h (61%) **17h** (7%)
6i (51%) **17i** (18%)

Scheme 6.

respectively, while 0.09% of cyclopentanone exists in the enol form.[24] Aldol condensations favored by enol formation enhance the formation of amides; this causes pyrimidines to be formed in lower yields.

When the reaction was carried out with nitriles substituted with electron donating groups such as methyl and methoxy (**4f–i**), the corresponding benzyl pyrimidines (**6f–i**) were isolated together with a significant amount of 2-substituted cyclopentanones **17f–i** (Scheme 6).

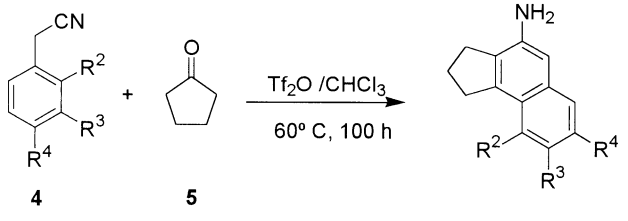
Isolation of compounds such as **17** from the reaction of ketones and nitriles with triflic anhydride has not been reported to date. Their IR spectra included bands corresponding to a carbonyl conjugated with a double bond at $\sim$1630 cm^{-1} and an exocyclic double bond at $\sim$1510 cm^{-1}. Bands for a NH_2 group at $\sim$3300 and 3200 cm^{-1} corresponded to two broad singlets at δ 9.35 and 4.65, respectively, signals in the ^1H NMR. This chemical shift difference was attributed to the existence of an intramolecular hydrogen bond between one of the protons of the amino group and the carbonyl group resulting a chelated structure (consistent with the low wavenumber value of the conjugated carbonyl absorption). NOE experiments confirmed the structure of **17**. For compounds **17f** and **17h** the relative position of the phenyl ring was determined by irradiation of the protons of the methyl and methoxy groups and observation of the NOE effect on the protons of the methylene group at the C-3 position of the cyclopentanone ring (Scheme 7).



17f and **17h**

Scheme 7.

The formation of **17** could be explained by a change in the reactivity of the cyano group of the benzyl nitrile brought about by a change in the electronic nature of the substituents attached at the phenyl ring. More electron donating substituents on the ring should cause the cyano group's electrophilic atom to be the carbon rather than the nitrogen. But in fact the reaction with nitriles bearing two and three methoxy groups (**4j–k**) produced neither pyrimidines nor compounds like **17**. Instead only cyclopentane fused naphthalene amines **18** were isolated (Scheme 8). These results confirm



4 **5**

j; R^2 = H; R^3 = R^4 = OCH_3
k; R^2 = R^3 = R^4 = OCH_3

18j (23%)
18k (20%)

Scheme 8.

that the mechanism of the reaction is controlled by the electronic nature and number of the substituents attached at the benzyl ring.

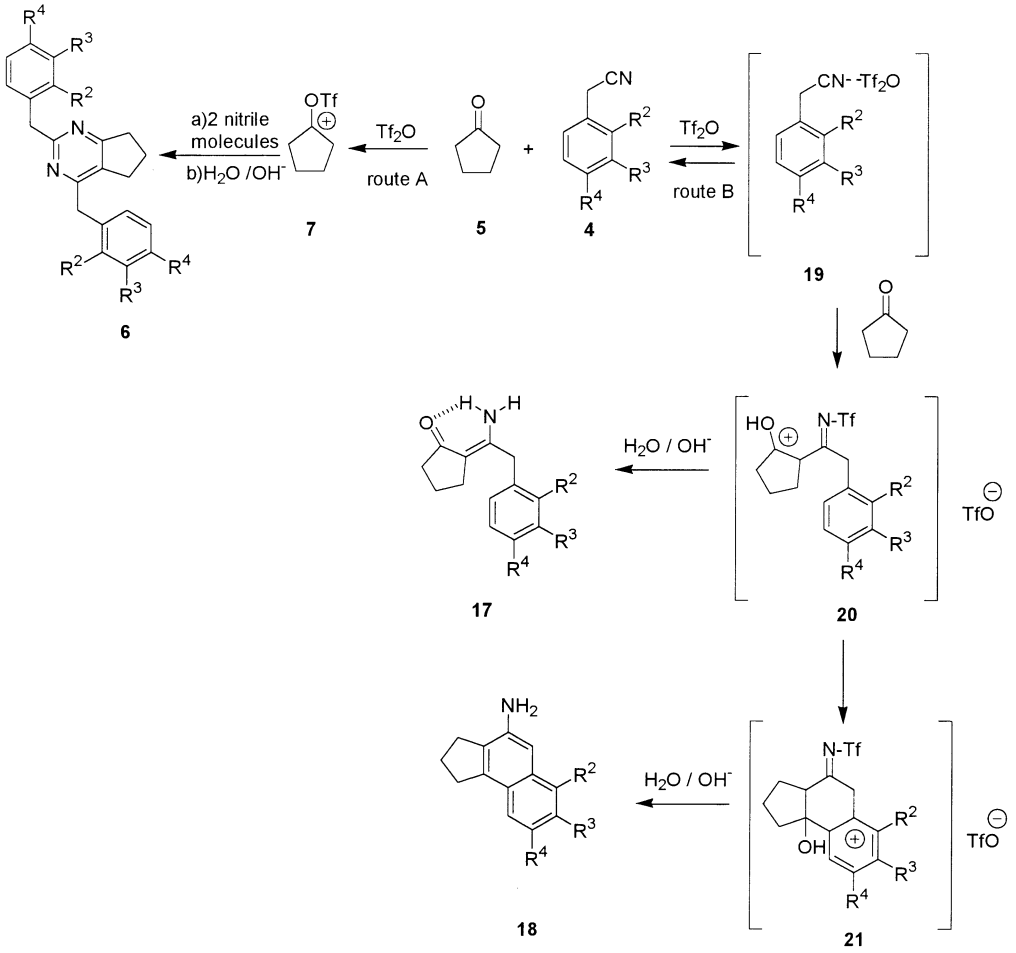
These findings allow us to postulate a new and general mechanism (Scheme 9) for the reaction of ketones with benzyl nitriles. This mechanism presents two different alternatives. The first one is the well known electrophilic attack of the triflic anhydride on the carbonyl group (route A) to form a trifliloxycarbenium ion (**7**).[18] Reaction of this ion with two nitrile molecules followed by basic hydrolysis leads to the formation of benzyl pyrimidines (**6**), which are the expected products for this process. This mechanism pathway takes place easily when R^2, R^3 and R^4 are hydrogen or electron withdrawing groups such as Cl or NO_2, that suppress the nucleophilic character of nitriles. The second alternative (route B) prevails when the substituents are groups such as methyl or methoxy. In this case the triflic anhydride attacks the nitrogen atom of the cyano group to form the complex **19**.

The electrophilic character of the carbon atom of the cyano group is enhanced by the reaction with Tf_2O. Thus, the reaction of **19** with cyclopentanone affords the intermediate **20** which after basic hydrolysis yields the substituted cyclopentanones **17**. This reaction takes place with benzyl nitriles bearing one methyl or one methoxy group. The number of electron donating groups attached at the phenyl ring of benzyl nitriles enhances the reactivity of the intermediate **20**. An intramolecular cyclization takes place forming **21** which after aromatization and basic hydrolysis yields the corresponding naphthalene amines **18**.

Triflic acid and aliphatic nitriles react slowly affording nitrilium salts.[25] Nitrilium salts can be also prepared from nitriles and methyl triflate,[26] or by reaction of nitriles with alkyl chloroformates in the presence of Lewis acid like pentachloro antimonate.[27] The nitrilium salts are well-known intermediates in organic synthesis.[28,29]

To determine the nature and structure of the reaction intermediate **19**, we carried out the reaction with several combinations of temperature, solvents and nucleophiles. In all case we were not able to isolate a nitrilium salt or a product likely to have emerged from a nitrilium salt. The ^{13}C NMR spectra of the reaction mixture between Tf_2O and a benzyl nitrile bearing electro donating groups reveals a small shielding ($\Delta\delta$=−2 ppm) of the carbon atom of the cyano group. The other carbon atoms were not affected. The carbon atom of the triflic anhydride appears as a quartet centered at 118.25 ppm with a coupling constant ^1J(C,F) of 322.2 Hz. No changes were observed in the ^{13}C NMR spectra after two weeks at room temperature in sealed tube. The presence of the CF_3 group in nitrilium salts appears[30] as two signals corresponding to the covalent and ionic forms of TfO, respectively, at 119.2 and 122.2 ppm. The signal for the nitrogen atom in the nitrilium salt is reported[25] to be split into a triplet due to the $^{13}C–^{14}N$ coupling.

The above data indicate that the reaction between Tf_2O and benzyl nitriles does not produce isolable nitrilium salts. The reaction of triflic anhydride and benzyl nitrile should afford a non-isolable complex (**19**) in equilibrium with the reactants.



Scheme 9.

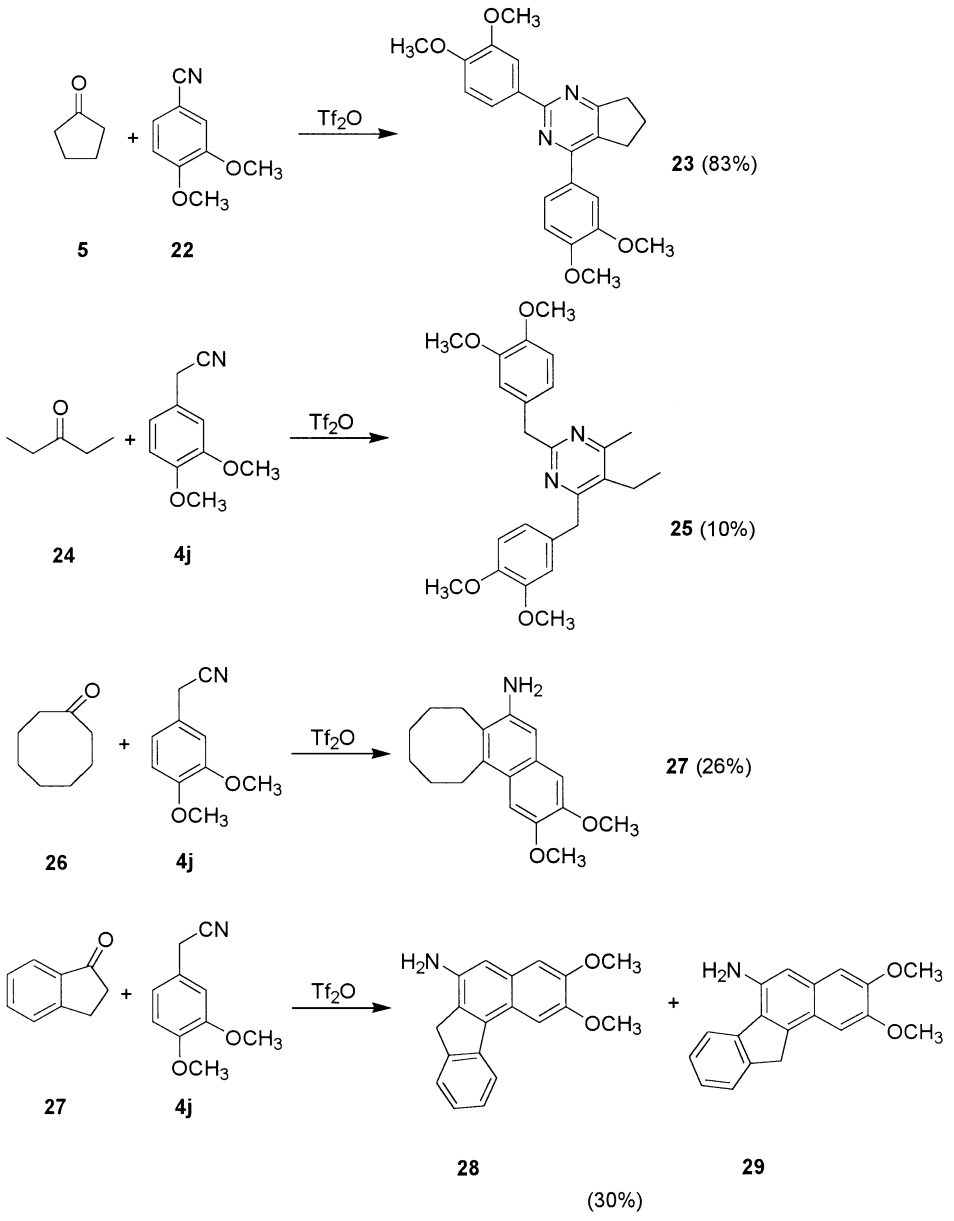
This complex reacts further if it is reactive toward electrophiles. Electron acceptor groups attached at the phenyl ring prevent the formation of the complex (**19**) and the final products are the pyrimidines (**6**). In contrast, benzyl nitriles having electron donor groups lead to a stabilized complex (**19**) which reacts with cyclopentanone to form compounds like **17** that then cyclize to form napthalene amines **18**.

Noteworthy are the poor yields obtained in the formation of compounds **17** and **18**. This can be attributed to the stability of the complex **19** even at high temperatures. After the basic hydrolysis used in the last step of the work-up of these reactions, significant amounts of unreacted nitriles accompany **17** and **18**. The recovered nitrile and the absence of the expected pyrimidines are probably due to the low reactivity of complex **19**. In this regard the recovered nitrile could be formed in the basic hydrolysis of the unreacted complex **19**. The nitrile is recovered even after long reaction times.

In some cases, the naphthalene amines **18** were isolated as their *N*-methyl derivatives; these were clearly formed by a methylating agent in the reaction mixtures. It is known that triflic anhydride reacts with alkoxy groups yielding alkyl triflates,[31] which are very powerful alkylating reagents.[18] In the present case, triflic anhydride can react with methoxy substituted benzyl nitriles to form methyl triflate which then converts the naphthalene amines in their *N*-methyl derivatives.

There are other features of the reaction mechanism besides the low reactivity of the complex **19**. When the reaction is carried out with 3,4-dimethoxyphenyl nitrile **22** the only isolated product was the corresponding arylpyrimidine **23** (Scheme 10). This could indicate that the cyclization process from the complex **19** requires a chain length of at least two carbon atoms and a nitrogen atom. Without this chain, the intermediates **19**–**21** cannot cyclize and the route A of the mechanism prevails. Aliphatic ketones such as 3-pentanone also afford pyrimidines (**25**) because the alkyl chain's flexibility prevents formation of stable intermediates with the ability to cyclize. Other cyclic ketones like cyclooctanone (**26**) and 1-indanone (**28**) react with methoxy substituted benzyl nitriles affording the corresponding naphthalene amines (**27** and **29**).

We conclude that these results clarify the mechanism of the reaction of ketones and nitriles. Thus, benzyl nitriles with electron acceptor groups afford benzyl pyrimidines. In contrast, benzyl nitriles with electron donor groups react through a different mechanism, which involves the formation of amino ketones intermediates. The last step of this reaction affords substituted naphthalene amines. The determination of the product is controlled by the nature and



Scheme 10.

number of the substituents attached at the phenyl ring of benzyl nitriles.

3. Experimental

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from TfOH and redistilled twice prior to use.[18] Melting points were determined on a Gallenkamp apparatus and are uncorrected. NMR spectra were taken on a Bruker DPX 300 and Varian VXR at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C. Chemical shifts (δ_H and δ_C) are given to residual $CHCl_3$ (7.26 and 77.0 ppm, respectively). *J* values are in Hertz. Infrared spectra were taken on a Shimadzu FTIR 8300. Mass spectra were carried out on a HP 5989A quadrupole instrument at 70 eV with a source temperature of 250°C. The CI spectra were recorded using methane as reagent gas. Elemental analyses: Perkin–Elmer 2400 CHN. X-Ray analysis were recorded on a Smart CCD-Bruker diffractometer with graphite monochromated Mo K_α radiation (λ=0.71073 Å). TLC analyses were performed on silica gel $60F_{250}$ plates and column chromatography was carried out on silica gel 60 (70–230 mesh). Reaction solvents were distilled from appropriate drying agent before use. X-Ray crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 174991.

3.1. Preparation of 2,4-dibenzyl pyrimidines 6, general procedure

A solution of Tf_2O (2.01 g, 7.13 mmol) in $CHCl_3$ (15 mL) was added dropwise to a stirred solution of ketone (6 mmol) and nitrile **4** (6.85 mmol) in $CHCl_3$ (10 mL) at room

temperature. The mixture was refluxed for the appropriate time. The formation of pyrimidines can be monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until it was basic. The organic layer was separated, washed with brine, dried ($MgSO_4$), and the solvent eliminated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate 7:3 as eluent. The corresponding pyrimidines were distilled or recrystallized.

3.1.1. 2,4-Dibenzyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6a. Reaction time: 24 h. Purification of crude product by column chromatography affords 0.87 g (83%) of title compound as viscous yellow oil, bp 250°C/0.1 Torr (kugelrohr); ν (film) 1562, 1493, 1391, 750, 700 cm^{-1}; δ_H ($CDCl_3$) 1.91 (q, 2H, J=7.7 Hz, CH_2), 2.67 (t, 2H, J=7.7 Hz, CH_2), 2.86 (t, 2H, J=7.7 Hz, CH_2), 4.00 (s, 2H, CH_2–Ar), 4.32 (s, 2H, CH_2–Ar), 7.12–7.46 (m, 10H, Ar–H); δ_C ($CDCl_3$) 21.75, 28.02, 34.04 (CH_2), 42.22, 45.79 (CH_2–Ar), 126.28, 126.56, 128.32, 128.51, 129.05, 129.14, 130.16, 137.52, 139.11, 163.34, 167.89, 175.07 (arom.); *m/z* (EI, 70 eV): 300 ($M^{\cdot+}$, 94), 299 (100), 272 (10), 91 (13); Anal. Calcd for $C_{21}H_{20}N_2$: C 83.96, H 6.71, N 9.33%, found C 84.15, H 7.05, N 9.25.

3.1.2. 2,4-Bis(4-chlorobenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6b. Reaction time 24 h. Purification of crude product by column chromatography affords 2.15 g (97%) of a white solid, mp 89–90°C (EtOH); ν (KBr): 1560, 1491, 1389, 1090, 850 cm^{-1}; δ_H ($CDCl_3$) 2.05 (q, 2H, J=7.7 Hz, CH_2), 2.77 (t, 2H, J=7.7 Hz, CH_2), 2.93 (t, 2H, J=7.7 Hz, CH_2), 3.98 (s, 2H, CH_2–Ar), 4.20 (s, 2H, CH_2–Ar), 7.11–7.30 (m, 8H, Ar–H); δ_C ($CDCl_3$) 21.81, 28.01, 34.06 (CH_2), 41.38, 44.96 (CH_2–Ar), 128.38, 128.61, 130.31, 130.43, 130.27, 132.13, 132.46, 135.86, 137.35, 162.87, 167.49, 175.40 (arom.); *m/z* (EI, 70 eV): 368 ($M^{\cdot+}$, 100), 333 (M−Cl, 6), 125 (9); Anal. Calcd for $C_{21}H_{18}Cl_2N_2$: C 68.30, H 4.91, N 7.59%, found C 68.05, H 5.10, N 7.35.

3.1.3. 2,4-Bis(4-nitrobenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6c. Reaction time 89 h. Purification of crude product by column chromatography affords 1.13 g (85%) of a white solid, mp 150–151°C (EtOH); ν (KBr): 1580, 1560, 1522, 1344 cm^{-1}; δ_H ($CDCl_3$) 2.10 (q, 2H, J=7.6 Hz, CH_2), 2.81 (t, 2H, J=7.6 Hz, CH_2), 2.96 (t, 2H, J=7.6 Hz, CH_2), 4.10 (s, 2H, CH_2–Ar), 4.32 (s, 2H, CH_2–Ar), 7.35–7.52 (AA′XX′, 4H, Ar–H), 8.12–8.16 (AA′XX′, 4H, Ar–H); δ_C ($CDCl_3$) 21.84, 28.04, 34.09 (CH_2), 41.62, 45.35 (CH_2–Ar), 123.54, 123.73, 129.86, 129.98, 130.76, 144.85, 146.30, 161.87, 166.71, 175.98 (arom.); *m/z* (EI, 70 eV): 390 ($M^{\cdot+}$, 100), 389 (80), 324 (11); Anal. Calcd for $C_{21}H_{18}N_4O_4$: C 64.61, H 4.65, N 14.35%, found C 63.99, H 4.71, N 13.90.

3.1.4. 2,4-Bis(3,4-dichlorobenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6d. Reaction time 24 h. Purification of crude product by column chromatography affords 1.32 g (88%) of a white solid, mp 71.5–72.5°C (EtOH); ν (KBr): 1564, 1470, 1391 cm^{-1}; δ_H ($CDCl_3$) 2.08 (q, 2H, J=7.7 Hz, CH_2), 2.81 (t, 2H, J=7.7 Hz, CH_2), 2.95 (t, 2H, J=7.7 Hz, CH_2), 3.93 (s, 2H, CH_2–Ar), 4.15 (s, 2H, CH_2–Ar), 7.05 (dd, J=8.3, 2.2 Hz, 1H, Ar–H), 7.18 (dd, J=8.3, 2.2 Hz, 1H, Ar–H), 7.31 (d, J=2.2 Hz, 1H, Ar–H), 7.32 (s, 1H, Ar–H), 7.36 (s, 1H, Ar–H), 7.44 (d, J=2.2 Hz, 1H, Ar–H); δ_C ($CDCl_3$) 21.82, 28.01, 34.09 (CH_2), 40.88, 44.64 (CH_2–Ar), 128.42, 128.59, 130.19, 130.40, 130.41, 130.88, 131.00, 132.15, 132.46, 137.49, 138.94, 162.23, 167.03, 175.69 (arom.); *m/z* (EI, 70 eV): 436 ($M^{\cdot+}$, 100), 435 (67), 401 (M−Cl, 8); Anal. Calcd for $C_{21}H_{16}Cl_4N_2$: C 57.56, H 3.68, N 6.39%, found C 57.22, H 3.33, N 6.09.

3.1.5. 2,4-Bis(2,4-dichlorobenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6e. Reaction time 47 h. Purification of the crude product by column chromatography affords 1.49 g (99%) of a white solid, mp 139–140°C (EtOH); ν (KBr): 1566, 1427, 1362, 1094, 1049 cm^{-1}; δ_H ($CDCl_3$) 2.18 (q, 2H, J=7.7 Hz, CH_2), 2.82 (t, 2H, J=7.7 Hz, CH_2), 2.97 (t, 2H, J=7.7 Hz, CH_2), 4.03 (s, 2H, CH_2–Ar), 4.29 (s, 2H, CH_2–Ar), 7.06–7.11 (m, 4H, Ar–H), 7.33 (s, 1H, Ar–H), 7.34 (s, 1H, Ar–H); δ_C ($CDCl_3$) 21.90, 28.02, 34.14 (CH_2), 38.19, 42.27 (CH_2–Ar), 126.69, 126.88, 128.94, 128.96, 132.11, 132.37, 132.59, 133.00, 133.98, 134.72, 135.22, 135.35, 161.60, 166.27, 175.28 (arom.); *m/z* (EI, 70 eV): 436 ($M^{\cdot+}$, not observed), 401 (M−Cl, 100), 148 (20); *m/z* (CI, CH_4): 437 (MH^+, 82); Anal. Calcd for $C_{21}H_{16}Cl_4N_2$: C 57.56, H 3.68, N 6.39%, found C 57.25, H 3.11, N 6.88.

3.1.6. 2,4-Dibenzyl-5,6,7,8-tetrahydroquinazoline 12. Reaction time 23 h. Purification by column chromatography of the crude product affords 0.72 g (45%) of a pale yellow oil, bp 250°C /0.1 Torr (kugelrohr); ν (film): 1555, 1490, 1390, 750, 700 cm^{-1}; δ_H ($CDCl_3$) 1.68–1.75 (m, 4H, CH_2), 2.57 (t, 2H, J=5.7 Hz, CH_2), 2.81 (t, 2H, J=5.7 Hz, CH_2), 4.04 (s, 2H, CH_2–Ar), 4.23 (s, 2H, CH_2–Ar), 7.14–7.38 (m, 10H, Ar–H); δ_C ($CDCl_3$) 22.02, 22.37, 24.42, 32.30 (CH_2), 40.98, 45.40 (CH_2–Ar), 126.22, 126.41, 128.25, 128.43, 128.84, 129.10, 137.40, 139.00, 165.80, 165.91, 166.30 (arom.); *m/z* (EI, 70 eV): 314 ($M^{\cdot+}$, 100), 313 (96), 299 (16), 91 (22); Anal. Calcd for $C_{22}H_{22}N_2$: C 84.04, H 7.05, N 8.91%, found C 83.55, H 6.19, N 8.08.

3.1.7. *N*-[2′-Oxo-1,1′-bi(cyclohexyl)-1-yl]-2-phenylacetamide 13. Purification of crude product by column chromatography affords 0.25 g (15%) of a white solid, mp 113–114°C (hexane); ν (KBr): 3333, 1709, 1643, 1541 cm^{-1}; δ_H ($CDCl_3$) 1.10–2.29 (m, 18H), 3.25 (dd, J=13.2, 4.8 Hz, 1H, CH), 3.48 (s, 2H, CH_2CONH), 5.45 (bs, 1H, NH), 7.24–7.35 (m, 5H, Ar–H); δ_C ($CDCl_3$) 21.33, 21.41, 25.50, 25.72, 28.43, 29.33, 30.32, 30.98 (CH_2), 43.87 (CH_2CO), 45.17 (CH_2CONH), 127.20, 128.90, 129.32, 135.45 (arom.), 170.26 (CONH), 212.42 (CO); *m/z* (EI, 70 eV): 313 ($M^{\cdot+}$, 14), 178 (81), 136 (50), 98 (100), 91 (54); Anal. Calcd for $C_{20}H_{27}NO_2$: C 76.64, H 8.68, N 4.47%, found C 76.76, H 8.33, N 4.29.

3.1.8. 2,4-Bis(2-methylbenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6f. Reaction time 90 h. Purification of crude product by column chromatography affords 0.83 g (74%) of a viscous yellowish oil, bp 250°C/0.1 Torr (kugelrohr); ν (film): 1564, 1387, 745 cm^{-1}; δ_H ($CDCl_3$) 1.88 (q, 2H, J=7.7 Hz, CH_2), 2.12 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.57 (t, 2H, J=7.7 Hz, CH_2), 2.82 (t, 2H, J=7.7 Hz, CH_2), 3.91 (s, 2H, CH_2–Ar), 4.16 (s, 2H,

CH_2–Ar), 6.90–7.10 (m, 8H, Ar–H); δ_C ($CDCl_3$) 19.98, 20.05 (CH_3), 21.92, 28.27, 34.13 (CH_2), 40.13, 43.26 (CH_2–Ar), 125.78, 125.85, 126.40, 126.72, 129.73, 129.91, 130.07, 130.12, 130.32, 135.98, 136.96, 137.07, 137.65, 163.25, 167.82, 175.02 (arom.); *m/z* (EI, 70 eV): 328 ($M^{\cdot+}$, 100), 313 (33), 299 (18); Anal. Calcd for $C_{23}H_{24}N_2$: C 84.11, H 7.36, N 8.53%, found 83.79, H 7.45, N 8.88.

3.1.9. (2*Z*)-2-[1-Amino-2-(2-methylphenyl)-1-ethylidene]-cyclopentanone 17f. Reaction time 90 h. Purification of crude product by column chromatography affords 0.23 g (18%) of yellow needles, mp 107–108°C (toluene/hexane); ν (KBr): 3283, 3094, 1628, 1515, 737 cm^{-1}; δ_H ($CDCl_3$) 1.81 (q, 2H, *J*=7.6 Hz, CH_2), 2.18 (s, 3H, CH_3), 2.28 (t, 2H, *J*=7.6 Hz, CH_2), 2.53 (t, 2H, *J*=7.6 Hz, CH_2), 3.46 (s, 2H, CH_2–Ar), 4.54 (bs, 1H, NH), 7.05–7.15 (m, 4H, Ar–H), 9.40 (bs, 1H, NH); δ_C ($CDCl_3$) 19.46 (CH_3), 20.61, 27.11, 37.81 (CH_2), 39.90 (CH_2–Ar), 103.39 (C=C), 126.61, 127.92, 130.44, 130.79, 133.19, 137.44 (arom.), 156.60 (=C–NH_2), 204.36 (CO); *m/z* (EI, 70 eV): 215 ($M^{\cdot+}$, 100), 198 (M−NH_3, 51), 142 (71); Anal. Calcd for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51%, found C 77.78, H 7.23, N 6.21.

3.1.10. 2,4-Bis(4-methylbenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6g. Reaction time 46 h. Purification of crude product by column chromatography affords 0.80 g (71%) of a white solid, mp 55–56°C (hexane); ν (KBr): 1566, 1514, 1391, 1215, 745 cm^{-1}; δ_H ($CDCl_3$) 2.02 (q, 2H, *J*=7.6 Hz, CH_2), 2.33 (s, 6H, CH_3), 2.75 (t, 2H, *J*=7.6 Hz, CH_2), 2.92 (t, 2H, *J*=7.6 Hz, CH_2), 4.00 (s, 2H, CH_2–Ar), 4.23 (s, 2H, CH_2–Ar), 7.07–7.33 (m, 8H, Ar–H); δ_C ($CDCl_3$) 20.98, 21.00 (CH_3), 21.75, 28.01, 34.01 (CH_2), 45.84, 45.32 (CH_2–Ar), 128.85, 128.91, 128.94, 129.11, 129.95, 134.42, 135.57, 135.94, 136.01, 163.48, 168.01, 174.94 (arom.); *m/z* (EI, 70 eV): 328 ($M^{\cdot+}$, 100), 327 (99), 300 (11), 105 (16); Anal. Calcd for $C_{23}H_{24}N_2$: C 84.11, H 7.36, N 8.53%, found 84.45, H 7.11, N 8.63.

3.1.11. (2*Z*)-2-[1-Amino-2-(4-methylphenyl)-1-ethylidene]cyclopentanone 17g. Reaction time 46 h. Purification of crude product by column chromatography affords 0.18 g (14%) of yellow needles, mp 116–117°C (toluene/hexane); ν (KBr): 3300, 3190, 1628, 1508 cm^{-1}; δ_H ($CDCl_3$) 1.88 (q, 2H, *J*=7.6 Hz, CH_2), 2.34 (s, 3H, CH_3), 2.34 (t, 2H, *J*=7.6 Hz, CH_2), 2.58 (t, 2H, *J*=7.6 Hz, CH_2), 3.50 (s, 2H, CH_2–Ar), 4.65 (bs, 1H, NH), 7.05–7.18 (AA′BB′, 4H, Ar–H), 9.35 (bs, 1H, NH); δ_C ($CDCl_3$) 21.14 (CH_3), 20.60, 27.20, 39.18 (CH_2), 39.63 (CH_2–Ar), 103.53 (C=), 129.27, 129.74, 131.93, 137.09 (arom.), 157.03 (=C–NH_2), 204.66 (CO); *m/z* (EI, 70 eV): 215 ($M^{\cdot+}$, 100), 198 (M−NH_3, 48), 170 (17), 142 (33); Anal. Calcd for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51%, found C 77.55, H 8.09, N 6.44.

3.1.12. 2,4-Bis(2-methoxybenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6h. Reaction time 18 h. Purification of crude product by column chromatography affords 0.65 g (51%) of a yellow oil, bp 150°C/0.1 Torr (kugelrohr); ν (film): 1568, 1495, 1392, 1246, 1107, 752 cm^{-1}; δ_H ($CDCl_3$) 1.99 (q, 2H, *J*=7.7 Hz, CH_2), 2.72 (t, 2H, *J*=7.7 Hz, CH_2), 2.90 (t, 2H, *J*=7.7 Hz, CH_2), 3.74 (s, 6H, OCH_3), 4.07 (s, 2H, CH_2–Ar), 4.31 (s, 2H, CH_2–Ar), 6.75–6.85 (m, 4H, Ar–H), 7.05–7.25 (m, 4H, Ar–H); δ_C ($CDCl_3$) 21.91, 28.04, 34.16 (CH_2), 35.73, 39.35 (CH_2–Ar), 52.28, 55.41 (OCH_3), 110.25, 110.41, 120.28, 120.42, 126.21, 127.34, 127.71, 127.88, 130.13, 130.30, 130.42, 157.20, 157.44, 163.46, 167.78, 174.61 (arom.); *m/z* (EI, 70 eV): 360 ($M^{\cdot+}$, 10), 345 (5), 329 (M−OCH_3, 100), 297 (18) (11); Anal. Calcd for $C_{23}H_{24}N_2O_2$: C 76.64, H 6.71, N 7.77%, found 76.99, H 7.11, N 8.22.

3.1.13. (2*Z*)-2-[1-Amino-2-(2-methoxyphenyl)-1-ethylidene]cyclopentanone 17h. Reaction time 18 h. Purification of crude product by column chromatography affords 0.25 g (18%) of a yellow-brown undistillable oil; ν (film): 3346, 3200, 1634, 1504, 1246 cm^{-1}; δ_H ($CDCl_3$) 1.83 (q, 2H, *J*=7.5 Hz, CH_2), 2.27 (t, 2H, *J*=7.6 Hz, CH_2), 2.58 (t, 2H, *J*=7.6 Hz, CH_2), 3.47 (s, 2H, CH_2–Ar), 3.79 (s, 3H, OCH_3), 5.15 (bs, 1H, NH), 6.84–6.92 (m, 2H, Ar–H), 7.09–7.26 (m, 2H, Ar–H), 9.70 (bs, 1H, NH); δ_C ($CDCl_3$) 20.50, 27.17, 34.35 (CH_2), 39.09 (CH_2–Ar), 55.44 (OCH_3), 102.98 (C=), 110.66, 120.88, 124.04, 128.67, 130.73, 157.42 (arom.), 157.89 (=C–NH_2), 204.17 (CO); *m/z* (EI, 70 eV): 231 ($M^{\cdot+}$, 100), 214 (M−NH_3, 26), 200 (M−OCH_3, 17), 199 (25), 158 (37); *m/z* (CI, CH_4): 232 (MH^+, 100); Anal. Calcd for $C_{14}H_{17}NO_2$: C 72.70, H 7.41, N 6.06%, found C 71.73, H 8.23, N 5.55.

3.1.14. 2,4-Bis(4-methoxybenzyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 6i. Reaction time 42 h. Purification of crude product by column chromatography affords 0.75 g (61%) of a yellowish solid, mp 58–59°C (MeOH); ν (KBr): 1572, 1508, 1300, 1244 cm^{-1}; δ_H ($CDCl_3$) 2.01 (q, 2H, *J*=7.7 Hz, CH_2), 2.73 (t, 2H, *J*=7.7 Hz, CH_2), 2.90 (t, 2H, *J*=7.7 Hz, CH_2), 3.76 (s, 6H, OCH_3), 3.95 (s, 2H, CH_2–Ar), 4.18 (s, 2H, CH_2–Ar), 6.76–6.84 (AA′XX′, 4H, Ar–H), 7.11–7.33 (AA′XX′, 4H, Ar–H); δ_C ($CDCl_3$) 21.82, 28.05, 34.06 (CH_2), 41.39, 44.85 (CH_2–Ar), 55.20 (OCH_3), 113.71, 113.86, 129.94, 129.98, 130.00, 131.24, 158.11, 158.27, 163.67, 168.11, 175.02 (arom.); *m/z* (EI, 70 eV): 360 ($M^{\cdot+}$, 10), 359 (56), 345 (35), 252 (20); Anal. Calcd for $C_{23}H_{24}N_2O_2$: C 76.64, H 6.71, N 7.77%, found 76.55, H 6.35, N 7.55.

3.1.15. (2*Z*)-2-[1-Amino-2-(4-methoxyphenyl)-1-ethylidene]cyclopentanone 17i. Reaction time 42 h. Purification of crude product by column chromatography affords 0.10 g (7%) of a yellow undistillable oil; ν (film): 3468, 1641, 1508, 1246 cm^{-1}; δ_H ($CDCl_3$) 1.88 (q, 2H, *J*=7.5 Hz, CH_2), 2.34 (t, 2H, *J*=7.6 Hz, CH_2), 2.60 (t, 2H, *J*=7.6 Hz, CH_2), 3.47 (s, 2H, CH_2–Ar), 3.68 (s, 3H, OCH_3), 4.59 (bs, 1H, NH), 6.84–7.18 (AA′XX′, 4H, Ar–H), 9.34 (bs, 1H, NH); δ_C ($CDCl_3$) 20.49, 27.04, 39.04 (CH_2), 39.05 (CH_2–Ar), 55.27 (OCH_3), 103.31 (C=), 114.35, 126.68, 130.38, 157.12 (arom.), 158.81 (=C–NH_2), 204.55 (CO); *m/z* (EI, 70 eV): 231 ($M^{\cdot+}$, 100), 214 (M−NH_3, 75), 158 (72), 121 (57); Anal. Calcd for $C_{14}H_{17}NO_2$: C 72.70, H 7.41, N 6.06%, found C 71.89, H 7.11, N 6.29.

3.1.16. 7,8-Dimethoxy-2,3-dihydro-1*H*-cyclopenta[*a*]-naphthalene-4-amine 18j. Reaction time 100 h. Purification of crude product by column chromatography affords 0.35 g (23%) of a yellow solid which corresponds with the

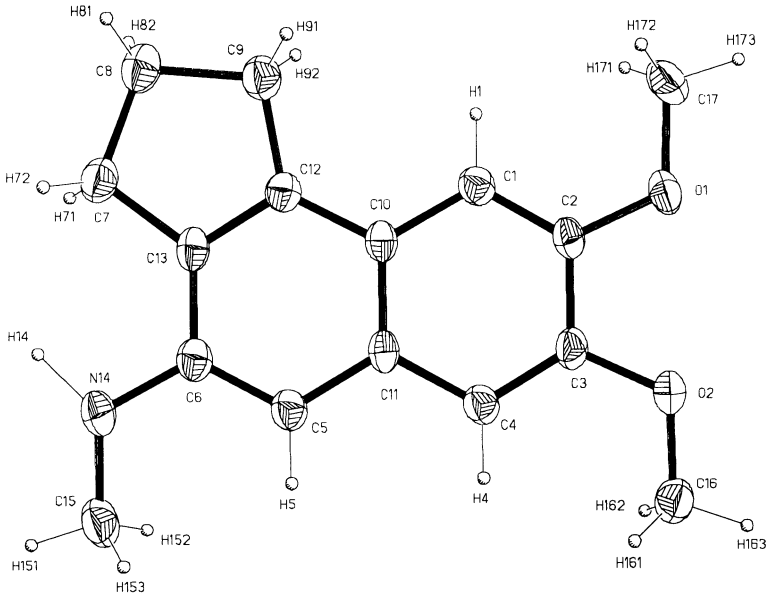


Figure 1. X-Ray structure of the *N*-methyl derivative of **18j**.

N-methyl derivative of **18j**, *N*-(7,8-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-4-yl)-*N*-methylamine. Yellow needles mp 199–201°C (EtOH); ν (KBr): 3393, 1525, 1469, 1407, 1250, 1155 cm^{-1}; δ_H ($CHCl_3$): 2.26 (q, *J*=7.5 Hz, 2H, CH_2), 2.86 (t, *J*=7.5 Hz, 2H, CH_2), 2.98 (s, 3H, CH_3NH), 3.21 (t, *J*=7.5 Hz, 2H, CH_2), 3.62 (bs, 1H, NH), 3.98 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.64 (s, 1H, Ar–H), 6.96 (s, 1H, Ar–H), 7.08 (s, 1H, Ar–H); δ_C ($CDCl_3$) 24.01, 30.22 (CH_2), 30.76 (CH_3NH), 31.69 (CH_2), 55.82, 55.69 (OCH_3), 101.27, 103.80, 105.81, 119.33, 128.62, 130.51, 139.09, 143.27, 146.51, 148.97 (arom.); *m/z* (EI, 70 eV): 257 ($M^{\cdot+}$, 100), 242 (77), 199 (25), 129 (24); *m/z* (CI, CH_4): 258 (MH^+, 100); Anal. Calcd for $C_{16}H_{19}NO_2$: C 76.67, H 7.45, N 5.45%, found C 73.36, H 7.29, N 5.31 (Fig. 1).

3.1.17. 7,8,9-Trimethoxy-2,3-dihydro-1*H*-cyclopenta[*a*]-naphthalene-4-amine 18k. Reaction time 170 h. Purification of crude product by column chromatography affords 0.33 g (20%) of a yellow undistillable oil. The spectroscopic data are consistent with the corresponding *N*-methyl derivative of **18k**, 4-methylamino-7,8,9-trimethoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene. ν (film): 3390, 1250, 1150 cm^{-1}; δ_H ($CHCl_3$): 2.05 (q, *J*=7.5 Hz, 2H, CH_2), 2.75 (t, *J*=7.5 Hz, 2H, CH_2), 2.82 (s, 3H, CH_3NH), 3.41 (t, *J*=7.5 Hz, 2H, CH_2), 3.70 (bs, 1H, NH), 3.98 (s, 3H, OCH_3), 3.81 (s, 6H, OCH_3), 6.46 (s, 1H, Ar–H), 6.67 (s, 1H, Ar–H); δ_C ($CDCl_3$) 24.30, 29.19 (CH_2), 30.57 (CH_3NH), 34.59 (CH_2), 55.62, 61.02, 61.28 (OCH_3), 101.18, 101.89, 115.21, 129.39, 133.28, 138.31, 138.68, 144.16, 149.45, 152.24 (arom.); *m/z* (EI, 70 eV): 287 ($M^{\cdot+}$, 89), 272 (100), 257 (M−$NHCH_3$, 21), 229 (24); Anal. Calcd for $C_{17}H_{21}NO_3$: C 71.06, H 7.37, N 4.87%, found C 70.22, H 7.00, N 3.89.

3.1.18. 2,4-Bis(3,4-dimethoxyphenyl)-6-7-dihydro-5*H*-cyclopenta[*d*]pyrimidine 23. Reaction time 40 h. Purification of crude product by column chromatography affords a yellow solid, mp 199–201°C (EtOH); ν (KBr): 1512, 1375, 1267, 1255 cm^{-1}; δ_H ($CDCl_3$) 2.18 (q, *J*=7.5 Hz, 2H, CH_2), 3.10 (t, *J*=7.5 Hz, 2H, CH_2), 3.23 (t, *J*=7.5 Hz, 2H, CH_2), 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 7.05–8.20 (m, 6H, Ar–H); δ_C ($CDCl_3$) 22.83, 31.18, 34.38 (CH_2), 55.94, 55.99 (OCH_3), 110.70, 110.76, 111.67, 121.29, 121.93, 127.52, 130.99, 131.33, 148.83, 149.00, 150.65, 150.90, 158.63, 162.58, 176.21 (arom.); *m/z* (EI, 70 eV): 392 ($M^{\cdot+}$, 100), 391 (60), 377 (15), 361 (M−OCH_3, 12), 346 (15); Anal. Calcd for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14%, found C 70.22, H 5.98, N 7.22.

3.1.19. 2,4-Bis(3,4-dimethoxybenzyl)-5-ethyl-6-methyl-pyrimidine 25. Purification of crude product afford by column chromatography 0.15 g (10%) of an undistillable oil. ν (film): 1514, 1259, 1028, 754 cm^{-1}; δ_H ($CDCl_3$) 1.25 (t, *J*=7.6 Hz, 3H, CH_3CH_2), 2.10 (s, 3H, CH_3), 2.65 (c, *J*=7.6 Hz, 2H, CH_2CH_3), 3.68 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3), 4.03 (s, 2H, CH_2–Ar), 4.16 (s, 2H, CH_2–Ar); δ_C ($CDCl_3$) 12.43 (CH_3CH_2), 12.98 (CH_3–Ar), 28.42 (CH_2CH_3), 45.03, 41.31 (CH_2–Ar), 55.66, 55.75, 55.83 (OCH_3), 110.97, 111.01, 111.93, 112.41, 120.60, 123.63, 120.93, 130.19, 131.67, 147.49, 147.62, 148.65, 148.92, 166.05, 166.43, 169.98 (arom.); *m/z* (EI, 70 eV): 422 ($M^{\cdot+}$, 100), 421 (39), 407 (70), 391 (M−OCH_3, 10); Anal. Calcd for $C_{25}H_{30}N_2O_4$: C 71.07, H 7.16, N 6.63%, found C 70.79, H 6.87, N 6.11.

3.1.20. 2,3-Dimethoxy-7,8,9,10,11,12-hexahydrocyclo-octa[*a*]naphthalene-6-amine 27. Purification of crude product by column chromatography affords 0.20 g (15%) of brown needles, mp 158.5–159.5°C (MeOH); ν (KBr): 3348, 3209, 1512, 1252, 1157 cm^{-1}; δ_H ($CDCl_3$) 1.35–1.79 (m, 8H, CH_2), 2.88 (t, *J*=6.2 Hz, 2H, CH_2–Ar), 3.18 (t, *J*=6.2 Hz, 2H, CH_2–Ar), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.87 (s, 1H, Ar–H), 6.91 (s, 1H, Ar–H), 7.22 (s, 1H, Ar–H); δ_C ($CDCl_3$) 26.21, 26.31, 26.97, 27.02, 29.63, 30.06 (CH_2), 55.68, 55.85 (OCH_3), 103.77, 105.33, 108.15, 121.61, 126.18, 129.44, 135.79, 140.85, 147.04, 148.99 (arom.); *m/z* (EI, 70 eV): 285 ($M^{\cdot+}$, 100), 270 (53); Anal. Calcd for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, N 4.91%, found C

75.25, H 8.00, N 5.11. The column chromatography also affords 0.15 g (11%) of the corresponding *N*-methyl derivative of **27**, *N*-(2,3-dimethoxy-7,8,9,10,11,12-hexahydrocycloocta[*a*]naphthalene-6-yl)-*N*-methylamine as a yellow solid, mp 164–165°C (MeOH); ν (KBr): 3429, 1510, 1244 cm^{-1}; δ_H ($CDCl_3$) 1.35–1.80 (m, 8H, CH_2), 2.87 (t, J=6.7 Hz, 2H, CH_2–Ar), 2.96 (s, 3H, CH_3NH), 3.20 (t, J=6.2 Hz, 2H, CH_2–Ar), 3.84 (s, 1H, NH), 3.98 (s, 6H, OCH_3), 6.71 (s, 1H, Ar–H), 7.02 (s, 1H, Ar–H), 7.23 (s, 1H, Ar–H); δ_C ($CDCl_3$) 25.68, 26.31, 26.98, 27.19, 29.47, 30.10 (CH_2), 31.33 (CH_3NH), 55.68, 55.91 (OCH_3), 102.53, 103.97, 105.94, 120.53, 125.66, 129.82, 135.18, 143.60, 146.59, 148.88 (arom.); *m*/*z* (EI, 70 eV): 299 ($M^{\cdot+}$, 100), 284 (62); Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68%, found C 76.25, H 8.55, N 4.55.

3.1.21. 2,3-Dimethoxy-7*H*-benzo[*c*]fluoren-6-amine 28 and 2,3-dimethoxy-11*H*-benzo[*a*]fluoren-6-amine 29. Purification of crude product by column chromatography affords a mixture 1:1 (determined by NMR) of **28** and **29** as an undistillable oil. ν (film): 3377, 1490, 1236, 1141 cm^{-1}; δ_H ($CDCl_3$) 3.78 (s, 2H, CH_2), 3.79 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.98–4.01 (m, 9H, OCH_3), 5.20 (bs, 4H, NH_2), 6.80 (s, 1H), 6.93 (s, 1H), 7.02 (s, 1H), 7.13 (s, 1H), 7.34 (t, J=7.5 Hz, 2H), 7.49 (t, J=7.5 Hz, 2H), 7.66 (d, J=7.5 Hz, 2H), 7.84 (s, 2H), 8.32 (d, J=7.5 Hz, 2H); δ_C (d_6-DMSO): 34.61, 34.63 (CH_2), 55.11, 55.42, 55.50 (OCH_3), 103.11, 103.22, 106.29, 107.05, 109.11, 117.57, 117.71, 122.18, 122.21, 124.82, 125.16, 125.27, 126.74, 126.76, 129.40, 129.84, 131.14, 131.49, 134.51, 141.36, 141.55, 142.48, 142.59, 143.60, 146.25, 146.32, 146.59, 148.53; *m*/*z* (EI, 70 eV): 291 ($M^{\cdot+}$, 100), 277 (77), 276 (53), 262 (43), 234 (43), 204 (24).

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