Lewis Acids as Mild and Effective Catalysts for the Synthesis of 3,5-Bis[(hetero)arylidene]piperidin-4-ones

by **Evgeniya Leonova**, **Mihail Makarov**, **Zinaida Klemenkova**, and **Irina Odinets***

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilova str., Moscow 119991, Russia (phone: +74991356166; fax: +74991355085; e-mail: odinets@ineos.ac.ru)

The aldol-crotonic condensation reactions of *N*-alkyl- and *N*H-piperidin-4-one derivatives with (hetero)aromatic aldehydes promoted by *Lewis* acids or bases were examined. This comparative study has revealed three effective catalytic systems based on *Lewis* acids, *i.e.*, $LiClO_4$ and $MgBr_2$ (in the presence of tertiary amine), and $BF_3 \cdot Et_2O$, for the synthesis of *N*-alkyl-substituted 3,5-bis(heteroarylidene)piperidin-4-ones, including those bearing acid- or base-labile groups both in the (hetero)aromatic groups and in the alkyl substituent at the N-atom. The highest reaction rate was observed for $LiClO_4$-mediated synthesis. Both $MgBr_2$- and $LiClO_4$-mediated syntheses were inefficient in the case of *N*H-piperidin-4-one, while $BF_3 \cdot Et_2O$ provided the final compounds in high yields. This catalyst is especially advantageous as it allows simultaneous condensation and deprotection in the case of *O*-protected piperidin-4-one.

1. Introduction. – In the last decade, derivatives of bis(heteroarylidene)cycloalkanones and the related bis(heteroarylidene)piperidin-4-ones attracted remarkable interest due to their high and diverse biological activities such as antiviral, antitumor, radical-scavenging, and antimutagen properties [1], as well as their application as ligands for the construction of coordination polymers [2]. Regarding the bioactivities, the conjugated 1,5-di(hetero)aryl-3-oxopenta-1,4-dienyl pharmacophore group in these compounds is assumed to interact with cellular constituents, since the nature of the (hetero)aryl substituents and those attached to the heterocyclic N-atom in the related piperidinone derivatives affects their potency.

The general synthetic approach to these cross-conjugated dienones is based on the crossed aldol-crotonic condensation of (hetero)aromatic aldehydes with alkanones or piperidin-4-ones, respectively, which proceeds under the action of strong bases (NaOH/EtOH) or protic acids (gaseous HCl/AcOH). Therefore, if the starting substrates bear acid- or base-labile substituents such as CN, $P(O)(OR)_2$, COOR, some heterocyclic moieties (*e.g.*, furanyl) *etc.*, the use of the above conditions would be unsuitable. Thus, several improvements have been achieved in the synthesis of bis(heteroarylidene)cycloalkanones by application of KF-supported reagents under microwave or ultrasonic irradiation [3], Pd/C-mediated synthesis [4], and *Lewis* acid catalysis including Me_3SiI (TMSI) [5], $Yb(OTf)_3$ [6], $LiClO_4$ in the presence of amines [7], and $MgBr_2 \cdot Et_2O$/MeOH/Et_3N [8], as well as SmI_3 [9] and $FeCl_3$ [10] in ionic liquids. Strangely enough, the data concerning improvements of the synthesis of 3,5-bis[(hetero)arylidene]piper-

idin-4-ones, which would be more advantageous for further modifications, are restricted to only one report on $LiClO_4$-mediated condensation of *N*H-piperidin-4-one with aromatic aldehydes and thiophene-2-carbaldehyde in the presence of Et_2NH and under solvent-free conditions [7]. The reported yields of the target *N*H-bis[(hetero)arylidene]piperidin-4-ones, achieved over 4 h, were in the range of 90–96%. However, in our hands, the attempt to use this procedure in the case of condensation of piperidin-4-one with 4-fluorobenzaldehyde gave less than 15% yield of the final product.

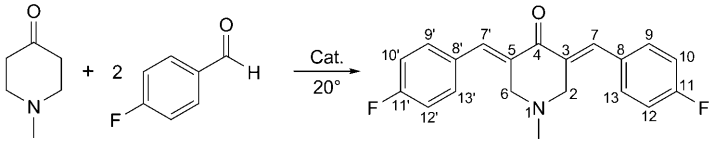
Therefore, to improve the synthesis of 3,5-bis[(hetero)arylidene]piperidin-4-ones bearing acid- or base-labile groups and to elaborate mild, effective, and reproducible procedures for their synthesis, it seems reasonable to undertake a detailed study on the applicability of *Lewis* acids and bases for the condensation of piperidin-4-one derivatives with (hetero)aromatic aldehydes. Here, we report the results of such comparative investigations, which revealed three effective catalytic systems based on *Lewis* acids.

2. Results and Discussion. – To estimate the activity of *Lewis* acids and bases as catalysts for aldol-crotonic condensation of piperidin-4-one derivatives with (hetero)-aromatic aldehydes, we tested catalytic systems based on *Lewis* acids such as lithium perchlorate ($LiClO_4$/$TMSNEt_2$), magnesium bromide ($MgBr_2 \cdot Et_2O$/MeOH/Et_3N), and $Yb(OTf)_3$, which provided high yields in the synthesis of 3,5-bis[(hetero)arylidene]cycloalkanones, as well as $BF_3 \cdot Et_2O$, silica-supported H_2SO_4 and trihexyl(tetradecyl)phosphonium chloride. As *Lewis* bases, Bu_3P and Ph_3P, useful as catalysts for the *Morita–Baylis–Hillman* reaction [11], intramolecular aldol condensations [12], and others, were also used. As a model, the reaction of *N*-methylpiperidin-4-one (**1a**) with 4-fluorobenzaldehyde was chosen as it allowed easy monitoring of the reaction course by ^{19}F-NMR spectroscopy. In *Table 1*, the results obtained for this reaction are collected.

Silica-supported H_2SO_4 significantly accelerates the reaction only when used in excess under solvent-free conditions (*Table 1*, *Entries 1* and *2*), while its application in a catalytic amount (20 mol-%) inhibited the reaction. Moreover, the condensation did not proceed when reactions using this catalyst were performed in CH_2Cl_2, MeCN, or EtOH solution, typically used in combination with silica-supported H_2SO_4. It should be noted that the sequence of reactant application on the catalyst played a crucial role: the product was formed only when the aldehyde was applied first.

In general, the catalysts, which provided excellent yields in the case of bis[(hetero)arylidene]cycloalkanone synthesis, exhibited lower activity for the condensation of **1a**. Thus, under otherwise equal conditions, the $Yb(OTf)_3$-catalyzed reaction afforded **2a** in low yields even at prolonged reaction time (*Table 1*, *Entries 3* and *4*). Similarly, the catalytic system $MgBr_2 \cdot Et_2O$/MeOH/Et_3N led to a moderate yield of 37% (63% according to the ^{19}F-NMR data) after 4 h, *i.e.*, the period of time provided more than 90% yields of bis[arylidene]cycloalkanones [8]. However, a longer reaction time (14 h) increased the yield up to 86% (97% according to the ^{19}F-NMR data; *Table 1*, *Entries 5* and *6*). More comparative results were achieved using the $LiClO_4$-based system, which provided 60% isolated yield of **2a** (91% according to the ^{19}F-NMR data) already after 4 h.

Table 1. *Condensation of* N-*Methylpiperidin-4-one* (**1a**) *with 4-Fluorobenzaldehyde in the Presence of* Lewis *Acids and Bases*



1a **2a**

Entry	Catalytic system	Solvent	Time [h]	Yield [%][a])
1	H_2SO_4/SiO_2 (6 equiv.)[b])	none	4	5 (12)
2	H_2SO_4/SiO_2 (6 equiv.)[b])	none	58	55
3	$Yb(OTf)_3$ (20 mol-%)	none	4	10 (22)
4	$Yb(OTf)_3$ (20 mol-%)	none	14	15 (34)
5	$MgBr_2 \cdot Et_2O$ (1 equiv.)/MeOH/Et_3N (2 equiv.)	none	4	37 (63)
6	$MgBr_2 \cdot Et_2O$ (1 equiv.)/MeOH/Et_3N (2 equiv.)	none	14	86 (97)
7	$LiClO_4$ (1 equiv.)/$TMSNEt_2$(2 equiv.)	none	4	60 (91)
8	$BF_3 \cdot Et_2O$ (9 equiv.)	$BF_3 \cdot Et_2O$	4	77[c])
9	$BF_3 \cdot Et_2O$ (4 equiv.)	THF	48	13[c])
10	$BF_3 \cdot Et_2O$ (4 equiv.)	CH_2Cl_2	48	51[c])
11	$BF_3 \cdot Et_2O$ (4 equiv.)	MeCN	48	66[c])
12	$BF_3 \cdot Et_2O$ (4 equiv.)[d])	MeCN	4	38 (56)[c])
13	$BF_3 \cdot Et_2O$ (4 equiv.)[d])	MeCN	9	67[c])
14	$(C_6H_{13})_3(C_{14}H_{29})P^+Cl^-$ (20 mol-%)	CH_2Cl_2	24	0
15	Ph_3P (20 mol-%)	MeCN	24	0
16	Bu_3P (20 mol-%)	MeCN	24	0

[a]) Yield of isolated **2a** (the yield according to the ^{19}F-NMR data is shown in parentheses). [b]) *w*/*w* Relative to *N*-methylpiperidin-4-one (**1a**). [c]) The product **2a** was isolated as HBF_4 salt. [d]) At 80°.

Rather good yields were achieved also in the presence of $BF_3 \cdot Et_2O$. As condensation results in the formation of two H_2O molecules, application of more than 2 equiv. of $BF_3 \cdot Et_2O$ was necessary. Moreover, the generation of tetrafluoroboronic acid resulted in the final product as a BF_4 salt. Therefore, 4 mol-equiv. of $BF_3 \cdot Et_2O$ were found to be optimal, and this reaction proceeded smoothly in solvents such as CH_2Cl_2 and MeCN, while THF inhibited the reaction (*Table 1*, *Entries 9–11*). In this context, MeCN is the solvent of choice, as it significantly shortens the reaction time when the reaction is performed at reflux. It also facilitates the workup due to low solubility of HBF_4 salt formed. The latter can be isolated *via* simple filtration. Finally, the reaction could be successfully performed in $BF_3 \cdot Et_2O$ as a sole solvent (*ca.* 9 equiv.), and just in this case the highest reaction rate was observed (*Table 1*, *Entry 8*).

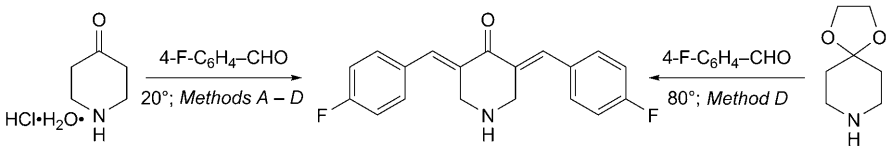
Neither phosphonium salts ($(C_6H_{13})_3(C_{14}H_{29})P^+Cl^-$) nor phosphines promoted the reaction. The phosphines underwent rapid oxidation to the corresponding phosphine oxides even under an inert atmosphere, apparently due to the reaction with aromatic aldehydes similar to results reported in the literature [13]. This study has revealed three catalytic systems of comparative potency, namely $LiClO_4$/$TMSNEt_2$ (*Method A*), $MgBr_2 \cdot Et_2O$/MeOH/Et_3N (*Method B*), and $BF_3 \cdot Et_2O$ (*Method C:* 9 equiv.; *Method*

D: 4 equiv of $BF_3 \cdot Et_2O$ in MeCN), which can be successfully used for aldol-crotonic condensation of **1a**. In the above model reaction, the systems provided excellent yields of the crude product **2a** according to the ^{19}F-NMR data; however, loss of the compound was observed during the purification procedures leading to **2a** of pharmaceutical grade.

To our surprise, both $MgBr_2$- and $LiClO_4$-mediated syntheses were inefficient in the case of *N*H-piperidin-4-one (**1b**) used as hydrochloride monohydrate (*Table 2*, *Entries 1–3*). Moreover, we failed to obtain 3,5-bis(4-fluorobenzylidene)piperidin-4-one (**3a**) in a reasonable yield using Et_2NH instead of Me_3SiNEt_2 in $LiClO_4$-mediated synthesis (*Table 2*, *Entry 3*). These data are in contrast to the reported procedure which led to more than 90% yield in the case of other aromatic aldehydes [8]. Better yields of **3a** were obtained using $BF_3 \cdot Et_2O$ either in combination with K_2CO_3 in MeCN solution or in excess (6 equiv.; 75 and 98% for the crude product, resp.; *Table 2*, *Entries 4* and *5*). Note that these reactions were performed at room temperature as heating accelerated mostly the side processes. Furthermore, $BF_3 \cdot Et_2O$ was especially advantageous for the condensation of the *O*-protected piperidin-4-one, 2,3-dioxa-8-azaspiro[4.5]decane (**1c**), as it provided a reasonable reaction rate at 80° along with simultaneous deprotection of the ketone group. It should be emphasized that such deprotection usually required application of strong acidic conditions [14] which affect adversely the labile groups (*Table 2*, *Entry 6*).

Application of the developed procedures for the condensation of **1a** and **1b** with other aromatic and heteroaromatic aldehydes (*Scheme*) afforded the corresponding *N*-methyl- or *N*H-3,5-bis[(hetero)arylidene]piperidin-4-ones **2b**–**2f**, and **3b** in good to high yields of isolated products. However, the yield of *N*-methyl-bis(pyridin-2-ylmethylidene)piperidin-4-one (**2g**) did not exceed 15%, when condensations of **1a** with pyridine-2-carbaldehyde were performed using the above mentioned systems. Moreover, we failed to obtain *N*H-bis(pyridin-2-ylmethylidene)piperidin-4-one. The

Table 2. *Condensation of N*H-*Piperidin-4-one* **1b** *and Its* O-*Protected Form* **1c** *with 4-Fluorobenzaldehyde in the Presence of Different Catalysts*



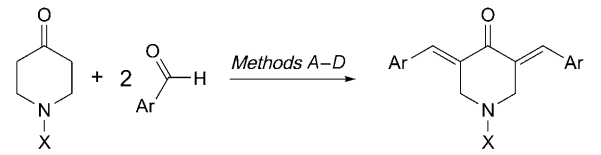
1b **3a** **1c**

Entry	Substrate	Catalytic system	Solvent	Time [h]	Yield [%][a])
1	**1b**	$MgBr_2 \cdot Et_2O$ (1 equiv.)/MeOH/Et_3N (2 equiv.)	none	14	8
2	**1b**	$LiClO_4$ (1 equiv.)/$TMSNEt_2$ (2 equiv.)	none	4	traces
3	**1b**	$LiClO_4$ (1 equiv.)/$HNEt_2$ (2 equiv.)	none	4	13
4	**1b**	$K_2CO_3/BF_3 \cdot Et_2O$ (4 equiv.)[b])	MeCN	24	34 (75)
5	**1b**	$BF_3 \cdot Et_2O$ (6 equiv.)[b])	MeCN	24	84 (98)
6	**1c**	$BF_3 \cdot Et_2O$ (4 equiv.)[b])[c])	MeCN	14	55

[a]) Yield of isolated **3a** (the yield according to the ^{19}F-NMR data is shown in parentheses). [b]) The product **3a** was isolated as HBF_4 salt. [c]) At 80°.

condensations of **1a** and **1b** with pyridine-2-carbaldehyde resulted mostly in complex mixtures of side-products where 1,2-di(pyridin-2-yl)ethane-1,2-dione was dominating. Note that such formal dimerization of pyridine-2-carbaldehyde in the presence of *Lewis* acids to afford the above mentioned 1,2-dione was reported in literature [15]. It should be noted that, if $BF_3 \cdot Et_2O$ was used as a catalyst and at least one of the reactants possesses poor solubility in this medium (*e.g.*, 4-nitrobenzaldehyde), it was more preferable to perform the reaction *via Method D* with MeCN as solvent.

Scheme



1a X = Me
1b X = H

	X	Ar
2b	Me	4-NO_2–C_6H_4
2c	Me	4-Me_2N–C_6H_4
2d	Me	4-NC–C_6H_4
2e	Me	Thiophen-2-yl
2f	Me	Pyridin-3-yl
2g	Me	Pyridin-2-yl
3b	H	4-NC–C_6H_4

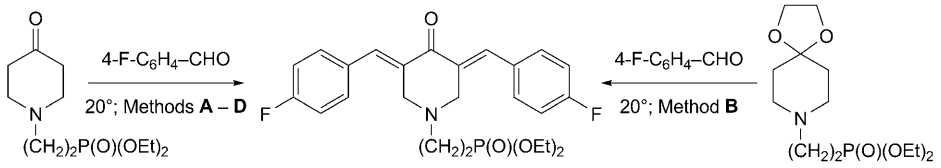
In general, the yields of 3,5-bis[(hetero)arylidene]-*N*-methylpiperidin-4-ones **2a**–**2g** depend both on the nature of the aldehyde and the catalytic system used. Thus, for $MgBr_2$-mediated synthesis (*Method B*) the yields decrease in the series 2-ThCHO > 4-F–C_6H_4CHO > 4-NC–C_6H_4CHO > 3-PyCHO. For reactions in the presence of $LiClO_4$ (*Method A*), the yield of the fluorinated compound **2a** sufficiently exceeded those for **2b**–**2f** which were approximately equal to each other. However, under other conditions being equal, the reaction in the presence of $LiClO_4$ proceeds faster than that using $MgBr_2$ and the comparable yields of the same product were achieved over 4 h ($LiClO_4$) *vs.* 14 h ($MgBr_2$).

When $BF_3 \cdot Et_2O$ was used in the condensation according to the *Scheme*, the yields of **2a**–**2f** decreased in a series of aldehydes as follows: 4-Me_2N–C_6H_4CHO > 4-O_2N–C_6H_4CHO > 4-F–C_6H_4CHO > 4-NC–C_6H_4CHO > 3-PyCHO > 2-ThCHO. In other words, no exact dependence on the electronic properties of the (hetero)aryl residue in the aldehyde was observed. When $BF_3 \cdot Et_2O$ was used as a solvent, the reaction rate at room temperature was even higher compared with that for the $LiClO_4$-mediated reaction, but substantially decreased when an additional co-solvent was used.

It is also a noteworthy observation of us that the CN group of 4-CN–C_6H_4CHO remained intact in the condensation with **1a** (compound **2d**) and *N*H-piperidin-4-one **1b** (compound **3b**) in the presence of the above-mentioned *Lewis* acids. It should be underlined that, under typical reaction conditions (gaseous HCl/AcOH), the reaction of **1b** with 4-NC–C_6H_4CHO is accompanied by hydrolysis of the CN functionality to yield the carbamoyl-substituted product (see *Exper. Part*).

Recently, we demonstrated that introduction of the alkyl phosphonate moiety at the N-atom of 3,5-bis[(hetero)arylidene]piperidin-4-ones resulted in a dramatic increase

Table 3. *Condensation of Diethyl 2-(4-Oxopiperidin-1-yl)ethylphosphonate* **1d** *and Its* O*-Protected form* **1e** *with 4-Fluorobenzaldehyde in the Presence of Different Catalysts*



1d **4** **1e**

Entry	Substrate	Catalytic system	Solvent	Time [h]	Yield [%][a])
1	**1d**	$MgBr_2 \cdot Et_2O$ (1 equiv.)/MeOH/Et_3N (2 equiv.)	none	14	30 (34)
2	**1d**	$LiClO_4$ (1 equiv.)/$TMSNEt_2$ (2 equiv.)	none	4	30 (32)
3	**1d**	$BF_3 \cdot Et_2O$ (6 equiv.)	MeCN	96	33 (52)
4	**1d**	$BF_3 \cdot Et_2O$ (9 equiv.)	$BF_3 \cdot Et_2O$	96	64 (86)
5	**1d**	$MgBr_2 \cdot Et_2O$ (1 equiv.)/MeOH/Et_3N (2 equiv.)	none	96	18
6	**1d**	$LiClO_4$ (1 equiv.)/$TMSNEt_2$ (2 equiv.)	none	96	33
7	**1e**	$BF_3 \cdot Et_2O$ (6 equiv.)	MeCN	96	16 (30)
8	**1e**	$BF_3 \cdot Et_2O$ (9 equiv.)	$BF_3 \cdot Et_2O$	96	56 (89)

[a]) Yield of isolated **4** (the yield according to the ^{19}F-NMR data is shown in parentheses).

of their cytotoxicity and bioavailability [16][17]. However, the syntheses of such phosphorylated compounds *via* the condensation of ω-aminophosphonates bearing piperidinone or a protected piperidinone moiety with aromatic aldehydes under the action of protic acids or strong bases resulted in rather low yields (typically in the range of 27–40%) of the products due to the presence of hydrolytically unstable ester groups at the P-atom [17]. Therefore, we tested the *Lewis* acid-mediated synthesis for aldol-crotonic condensation using β-aminophosphonates **1d**, **1e** and 4-fluorobenzaldehyde as model substrate (*Table 3*).

Similar to the reaction of *N*H-piperidin-4-one (**1b**), both $MgBr_2$- and $LiClO_4$-mediated syntheses provided quite low yields (*ca.* 30%) of the phosphorylated product **4** independent of the reaction time. When $BF_3 \cdot Et_2O$ was used, the reaction was rather sluggish in MeCN but provided the desired product **4** in good yields in the case of both phosphorylated substrates **1d** and **1e** using this *Lewis* acid in excess (*Table 3*, *Entries 4* and *8*). According the ^{31}P-NMR spectroscopy of the reaction mixtures, the hydrolysis of the ester groups at the P-atom was not observed, and the loss of product during the isolation procedure was connected with the typical retention of the phosphonates on silica gel.

3. Conclusions. – Aldol-crotonic condensation under the catalytic action of *Lewis* acids, present an effective approach to 3,5-bis[(hetero)arylidene]piperidin-4-ones including those bearing acid- or basic-labile groups. The catalytic system of choice depends both on the nature of the aldehyde and starting piperidone. $LiClO_4$- and $MgBr_2$-mediated syntheses are especially advantageous for the condensation of (hetero)aromatic aldehydes with *N*-alkylpiperidin-4-ones, while application of $BF_3 \cdot Et_2O$ is preferred in the case of *N*H- and *N*-(ω-phosphorylalkyl)piperidin-4-ones.

Moreover, the usage of $BF_3 \cdot Et_2O$ allows simultaneous condensation and deprotection of *O*-protected piperidin-4-ones along with easy isolation of the final products as BF_4 salts.

Experimental Part

1. *General.* All commercial reagents were used as purchased without further purification, all solvents were reagent grade. *Diethyl 2-(4-oxopiperidin-1-yl)ethylphosphonate* (**1d**) and *diethyl [2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)ethyl]phosphonate* (**1e**) were obtained according to known procedures [17]. The mixtures were stirred magnetically in round-bottomed flasks, and the reaction course was monitored by ^{19}F- or ^{31}P-NMR technique, or by TLC as appropriate. M.p.: *MPA 120 EZ-Melt* automated melting point apparatus; uncorrected. Anal. TLC: *Merck* silica gel *60* F_{254} plates; visualization by UV light. IR Spectra: in KBr pellets on a *Fourier*-transform spectrometer *Magna-IR750* (*Nicolet*), resolution 2 cm^{-1}, 128 scans. NMR Spectra: *Bruker AMX-400* spectrometer (^1H, 400.13; ^{19}F, 376.3; ^{31}P, 161.97; and ^{13}C, 100.61 MHz), using residual ^1H-signals and the ^{13}C-signal of a deuterated solvent as an internal standard rel. to TMS, and CF_3COOH (^{19}F) and H_3PO_4 (^{31}P) as an external standard; the ^{13}C-NMR spectra were recorded using the JMODECHO mode; the signals for the C-atom bearing odd and even numbers of H-atoms have opposite polarities; C-atom numbering used in the ^{13}C-spectra of 3,5-bis(benzylidene)piperidin-4-ones is shown in *Table 1*.

2. *Synthesis of 3,5-Bis[(hetero)arylidene]piperidin-4-ones in the Presence of* Lewis *Acids* (*General Procedures*): *Method A*. To a mixture of anh. $LiClO_4$ (1 mmol) and $TMSNEt_2$ (2 mmol), the corresponding aldehyde (2 mmol) and piperidin-4-one **1a**–**1e** (1 mmol) were added at r.t., and the mixture was stirred under these conditions until the consumption of the starting reactants (monitoring by NMR or TLC as appropriate). Then, H_2O (10 ml) was added to the mixture, followed by stirring for 30 min. The precipitate was filtered off and recrystallized from AcOEt or EtOH to afford the final 3,5-bis[(hetero)arylidene]piperidin-4-one.

Method B. The corresponding piperidin-4-one **1a**–**1e** (1 mmol) was added to a mixture of the desired aldehyde (2 mmol), MeOH (1 mmol), $MgBr_2 \cdot OEt_2$ (1 mmol), and Et_3N (2 mmol), and the resulting mixture was stirred at r.t. until the consumption of the starting reactants (monitoring by NMR or TLC when appropriate). Further workup was similar to that described in *Method A*.

Method C. A mixture of the corresponding piperidin-4-one **1a**–**1e** (1 mmol), aldehyde (2 mmol), and $BF_3 \cdot Et_2O$ (9 mmol) was stirred at r.t. The course of the reaction was monitored by TLC or NMR as appropriate. After completion of the reaction, the mixture was dissolved in hot EtOH. The soln. obtained was allowed to cool to r.t. The precipitate was filtered off and air-dried to give the final product as a BF_4 salt.

Method D. $BF_3 \cdot Et_2O$ (4 mmol) was added to a soln. of the corresponding aldehyde and piperidin-4-one **1a**–**e** (1 mmol) in 1 ml of MeCN. Then, the mixture was refluxed over an appropriate period of time (*Tables 1–3*) or under ambient conditions in the case of compound **4**. After chilling of the mixture to ambient temp., the precipitate formed was filtered off and recrystallized from EtOH to give the final 3,5-bis[(hetero)arylidene]piperidin-4-one as a BF_4 salt.

The structures of the known 3,5-bis[(hetero)arylidene]piperidin-4-ones **2a** [18], **2c** [19], **2e** [20], **2f** [21], and **3a** [22] obtained *via Methods A* and *B* as free bases were confirmed by the multinuclear NMR spectra. Their physicochemical constants fit well the available literature data. By *Methods C* and *D*, the products **2a**, **2b**, **2d**, **2f**, and **3a** were isolated as HBF_4 salts forming stable hydrates (see below). In the case of *(3*E*,5*E*)-bis[4-(dimethylamino)benzylidene]-1-methylpiperidin-4-one* (**2c**), *diethyl (3*E*,5*E*)-bis[(4-fluorobenzylidene)-4-oxopiperidin-1-yl]methylphosphonate* (**4**), and *(3*E*,5*E*)-bis(pyridin-2-ylmethylidene)-1-methylpiperidin-4-one* (**2g**), their HBF_4 salts were converted to the corresponding free bases *via* treatment with Na_2CO_3 soln.

Compound **2c** and its BF_4 salt represented a dark orange solid, all other products were isolated as yellow solids.

*(3*E*,5*E*)-3,5-Bis(4-fluorobenzylidene)-1-methyl-4-oxopiperidinium Tetrafluoroborate* (**2a** $\cdot HBF_4$). M.p. 220–224°. IR (KBr): 3081*w*, 1667*w* (C=O), 1610*m* (C=C), 1599*s*, 1588*m*, 1512*s*, 1470*w*, 1301*w*,

1281*w*, 1243*m*, 1200*m*, 1163*s*, 1106*s*, 1056*s*, 1030*s*, 981*w*, 844*w*, 836*m*, 530*m*, 495*m*. ^{1}H-NMR ((D$_6$)DMSO): 3.04 (*s*, MeN); 4.68 (*s*, 2 CH_2N); 7.40 (*dd*, ^3J(H,F) = ^3J(H,H) = 8.8, 4 H); 7.65 (*dd*, ^4J(H,F) = 5.7, ^3J(H,H) = 8.4, 4 H); 7.92 (*s*, 2 H–C=); 10.30 (*s*, HBF_4). ^{13}C-NMR ((D$_6$)DMSO): 42.98 (MeN); 53.92 (C(2), C(6)); 116.45 (*d*, ^2J(C,F) = 21.6, C(10), C(10′), C(12), C(12′)); 127.17 (C(3), C(5)); 130.42 (C(8), C(8′)); 133.69 (*d*, ^3J(C,F) = 8.6, C(9), C(9′), C(13), C(13′)); 139.07 (C(7), C(7′)); 163.36 (*d*, ^1J(C,F) = 249.8, C(11), C(11′)); 181.78 (C(4)). ^{19}F-NMR ((D$_6$)DMSO): –108.84; –147.98. Anal. calc. for $C_{20}H_{17}F_2NO \cdot HBF_4$ (422.17): C 58.14, H 4.39, N 3.39; found: C 58.11, H 4.21, N 3.21.

*(3*E*,5*E*)-1-Methyl-3,5-bis(4-nitrobenzylidene)-4-oxopiperidinium Tetrafluoroborate* (**2b** · HBF_4). Yield 80% (*Method D*). M.p. 233–235°. IR (KBr): 3435*m*, 3188*w*, 1675*w* (C=O), 1615*m* (C=C), 1598*m*, 1518*s*, 1347*s*, 1274*m*, 1200*w*, 1175*m*, 1119*m*, 1084*m*, 1058*m*, 856*w*. ^{1}H-NMR ((D$_6$)DMSO): 2.88 (*s*, MeN); 4.51 (*s*, 2 CH_2N); 7.81 (*d*, ^3J(H,H) = 8.8, 4 arom. H); 7.95 (*s*, 2 H–C=); 8.34 (*d*, ^3J(H,H) = 8.8, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 42.96 (MeN); 53.83 (C(2), C(6)); 124.16 (C(9), C(9′), C(13), C(13′)); 130.24 (C(3), C(5)); 132.08 (C(10), C(10′), C(12), C(12′)); 138.08 (C(8), C(8′)); 140.16 (C(11), C(11′)); 148.11 (C(7), C(7′)); 181.62 (C(4)). ^{19}F-NMR ((D$_6$)DMSO): –148.18. Anal. calc. for $C_{20}H_{17}N_3O_5 \cdot HBF_4 \cdot 0.75\ H_3BO_3$ (513.64): C 46.78, H 3.97, N 8.18; found: C 46.60, H 3.51, N 7.96.

*(3*E*,5*E*)-3,5-Bis[4-(dimethylamino)benzylidene]-1-methylpiperidin-4-one* (**2c**). The compound was isolated in 91% yield as the corresponding BF_4 salt *via* the *Method D*. After isolation, this hygroscopic product was immediately converted to the corresponding free base **2c** in 87% yield by the treatment with Na_2CO_3 soln. The precipitate of free base of **2c** was filtered off and dried over P_2O_5 under vacuum (20 mm Hg, 2 h).

*4,4′-[(1-Methyl-4-oxopiperidine-3,5-diylidene)di(*E*)methylylidene]dibenzonitrile* (**2d**).Yield 47% (*Method A*), 60% (*Method B*). M.p. >230° (dec.). Recrystallized from $CHCl_3$/MeOH. IR (KBr): 2946*w*, 2228*s* (CN); 1673*m* (C=O), 1616*s* (C=C), 1604*m*, 1584, 1501*w*, 1411*w*, 1331*w*, 1270*s*, 1184*s*, 1171*s*, 1127*w*, 1056*w*, 987*w*, 837*m*, 559*s*. ^{1}H-NMR ((D$_6$)DMSO): 2.46 (*s*, MeN); 3.72 (*s*, 2 CH_2N); 7.47 (*d*, ^3J(H,H) = 8.2, 4 H); 7.72 (*d*, ^3J(H,H) = 8.4, 4 H); 7.76 (*s*, 2 CH=). ^{13}C-NMR ((D$_6$)DMSO): 44.70 (MeN); 55.82 (C(2), C(6)); 111.14 (C(11), C(11′)); 118.24 (CN); 130.70 (C(9), C(9′), C(13), C(13′)); 132.18 (C(10), C(10′), C(12), C(12′)); 132.77 (C(7), C(7′)); 135.98 (C(3), C(5)); 139.01 (C(8), C(8′)); 186.21 (C(4)). Anal. calc. for $C_{22}H_{17}N_3O \cdot CHCl_3 \cdot MeOH$ (490.82): C 58.73, H 4.52, N 8.56; found: C 59.12, H 4.59, N 8.74.

*(3*E*,5*E*)-3,5-Bis(4-cyanobenzylidene)-1-methyl-4-oxopiperidinium Tetrafluoroborate* (**2d** · HBF_4). Yield 74% (*Method D*). M.p. 268–270°. IR (KBr): 3436*w*, 3140*m*, 2225*m* (CN); 1675*w* (C=O), 1619*s* (C=C), 1604*m*, 1586*m*, 1415*w*, 1290*w*, 1272*s*, 1198*w*, 1173*w*, 1083*s*, 1074*s*, 1026*s*, 941*w*, 833*m*, 555*m*. ^{1}H-NMR ((D$_6$)DMSO): 2.99 (*s*, MeN); 4.66 (*s*, 2 CH_2N); 7.75 (*d*, ^3J(H,H) = 8.3, 4 H); 7.95 (*s*, 2 H–C=); 8.03 (*d*, ^3J(H,H) = 8.4, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 42.64 (MeN); 53.53 (C(2), C(6)); 112.23 (C(11), C(11′)); 118.48 (CN); 129.52 (C(9), C(9′), C(13), C(13′)); 131.28 (C(10), C(10′), C(12), C(12′)); 132.70 (C(7), C(7′)); 138.12 (C(3), C(5)); 137.98 (C(8), C(8′)); 181.38 (C(4)). ^{19}F-NMR ((D$_6$)DMSO): –148.18. Anal. calc. for $C_{22}H_{17}N_3O \cdot HBF_4 \cdot 0.5\ H_2O$: C 60.55, H 4.13, N 9.63; found: C 61.11, H 3.92, N 9.59.

*(3*E*,5*E*)-1-Methyl-3,5-bis(thiophen-2-ylmethylidene)piperidin-4-one* (**2e**). Yield 50% (*Method A*), 90% (*Method B*), 50% (*Method D*, 7 d, r.t., isolated as a free base).

*(3*E*,5*E*)-1-Methyl-3,5-bis(pyridin-3-ylmethylidene)piperidin-4-one* (**2f**). Yield 52% (*Method A*), 50% (*Method B*).

*(3*E*,5*E*)-1-Methyl-4-oxo-3,5-bis(pyridin-3-ylmethylidene)piperidinium Tetrafluoroborate* (**2f** · HBF_4). Yield 60% (*Method D*). M.p. 148–158°. IR (KBr): 3436*m*, 3109*w*, 2922*w*, 2693*m*, 1691*w* (C=O), 1635*m* (C=C), 1602*w*, 1552*m*, 1467*m*, 1270*m*, 1211*m*, 1175*s*, 1084*s*, 1060*s*, 1034*s*, 980*m*, 939*w*, 804*w*, 767*w*, 678*m*, 534*m*, 522*m*. ^{1}H-NMR ((D$_6$)DMSO): 3.03 (*s*, MeN); 4.74 (*s*, 2 CH_2N); 7.80 (*dd*, ^3J(H,H) = 5.4, 2 H); 7.98 (*s*, 2 H); 8.24 (*d*, ^3J(H,H) = 8.1, 2 H); 8.80 (*d*, ^3J(H,H) = 7.7, 2 H); 8.92 (*s*, 2 H–C=); 10.35 (*s*, HBF_4). ^{13}C-NMR ((D$_6$)DMSO): 42.65 (MeN); 53.24 (C(2), C(6)); 127.04 (C of Py); 131.14 (C(7), C(7′)); 132.37 (C of Py); 134.56 (C of Py); 143.64 (C=*C*H–N), 144.64 (C(3), C(5)); 145.32 (*C*=CH–N), 180.95 (C(4)). Anal. calc. for $C_{18}H_{17}N_3O \cdot 3\ HBF_4 \cdot 1.5\ H_2O$ (581.81): C 37.16, H 3.98, N 7.22; found: C 36.98, H 3.65, N 7.21.

*(3*E*,5*E*)-1-Methyl-3,5-bis(pyridin-2-ylmethylidene)piperidin-4-one* (**2g**). Yield 12% (*Method A*), 8% (*Method B*), 15% (*Method D*). M.p. 135–137°. IR (KBr): 2940*w*, 2772*m*, 2761*m*, 1673*m* (C=O), 1618*m* (C=C), 1592*s*, 1579*s*, 1469*w*, 1430*m*, 1300*w*, 1276*s*, 1165*s*, 1060*w*, 980*w*, 923*w*, 785*m*, 738*m*, 544*m*.

^{1}H-NMR ($CDCl_3$): 2.52 (*s*, MeN); 4.16 (*s*, 2 CH_2N); 7.18 (*t*, ^3J(H,H) = 6.0, 2 H); 7.43 (*d*, ^3J(H,H) = 7.7, 2 H); 7.60 (*s*, 2 H−C=); 7.69 (*t*, ^3J(H,H) = 7.3, 2 H); 8.69 (*d*, ^3J(H,H) = 3.4, 2 H). ^{13}C-NMR ($CDCl_3$): 45.83 (MeN); 57.57 (C(2), C(6)); 122.56 (C of Py); 127.46 (C of Py); 132.37 (C(7), C(7′)); 136.19 (C of Py); 137.51 (C(3), C(5)); 149.46 (C=N−*C*H=); 154.95 (C=N−); 188.70 (C(4)). Anal. calc. for $C_{18}H_{17}N_3O$ (291.35): C 74.20, H 5.88, N 14.42; found: C 73.64, H 6.04, N 14.38.

*(3*E,5E*)-3,5-Bis(4-fluorobenzylidene)-4-oxopiperidinium Tetrafluoroborate* (**3a** · HBF_4). M.p. 233–236°. ^{1}H-NMR ((D$_6$)DMSO): 4.51 (*s*, 2 CH_2N); 7.37 (*dd*, ^3J(H,F) = ^3J(H,H) = 8.8, 4 H); 7.62 (*dd*, ^4J(H,F) = 5.8, ^3J(H,H) = 8.3, 4 H); 7.89 (*s*, 2 H−C=); 9.17 (*s*, NH, HBF_4). ^{13}C-NMR ((D$_6$)DMSO): 43.94 (C(2), C(6)); 115.71 (*d*, ^2J(C,F) = 21.3, C(10), C(10′), C(12), C(12′)); 127.49 (C(3), C(5)); 130.12 (*d*, ^4J(C,F) = 2.9, C(8), C(8′)); 132.68 (*d*, ^3J(C,F) = 8.8, C(9), C(9′), C(13), C(13′)); 137.97 (C(7), C(7′)); 162.88 (*d*, ^1J(C,F) = 250.2, C(11), C(11′)); 182.09 (C(4)). ^{19}F-NMR ((D$_6$)DMSO): −109.64; −148.16. Anal. calc. for $C_{19}H_{15}F_2NO \cdot HBF_4 \cdot 0.5\ H_2O$ (408.15): C 55.91, H 4.20, N 3.43; found: C 55.50, H 3.84, N 3.34.

*(3*E,5E*)-3,5-Bis(4-cyanobenzylidene)-4-oxopiperidinium Tetrafluoroborate* (**3b** · HBF_4). Yield 88% (*Method D*). M.p. >230° (dec.). IR (KBr): 3430*w*, 3198*w*, 3144*m*, 2226*s* (CN); 1682*m* (C=O), 1608*s*, 1605*s* (C=C), 1500*w*, 1410*m*, 1314*w*, 1290*s*, 1182*s*, 1168*m*, 1082*s*, 964*m*, 918*m*, 852*m*, 830*m*, 556*m*. ^{1}H-NMR ((D$_6$)DMSO): 4.57 (*s*, 2 CH_2N); 7.77 (*d*, ^3J(H,H) = 8.2, 4 H); 7.97 (*s*, 2 H−C=); 8.04 (*d*, ^3J(H,H) = 8.2, 4 H); 9.44 (*s*, NH, HBF_4). ^{13}C-NMR ((D$_6$)DMSO): 44.25 (C(2), C(6)); 112.31 (C(11), C(11′)); 118.71 (CN); 130.37 (C(9), C(9′), C(13), C(13′)); 131.30 (C(10), C(10′), C(12), C(12′)); 132.89 (C(7), C(7′)); 137.89 (C(3), C(5)); 138.41 (C(8), C(8′)); 182.37 (C(4)). Anal. calc. for $C_{21}H_{15}N_3O \cdot HBF_4$ (413.18): C 61.05, H 3.90, N 10.17; found: C 61.08, H 3.83, N 10.22.

*4,4′-{(4-Oxopiperidine-3,5-diylidene)di[(*E*)-methylidene]}dibenzamide.* *N*H-Piperidin-4-one (1 mmol) and 4-formylbenzonitrile (2 mmol) were dissolved in glacial AcOH (3 ml) · HCl (prepared from NH_4Cl, 5 mmol) was bubbled through the soln. The soln. was allowed to stay at r.t. for *ca.* 24 h. Then, the mixture was added to aq. $NaHCO_3$ (20 ml) and acetone (3 ml), followed by stirring over 0.5 h. The light-yellow precipitate was filtered off and recrystallized from DMSO. Yield 92%. M.p. >212° (dec.). IR (KBr): 3384*m* (NH_2), 3189*m* (NH_2), 1651*s* (C=O), 1613*m* (C=C), 1557*w*, 1417*m*, 1397*m*, 1259*w*, 1184*w*, 913*w*, 876*w*. ^{1}H-NMR ((D$_6$)DMSO): 4.05 (*s*, 2 CH_2N); 7.36 (*s*, 2 H−C=), 7.57 (*d*, ^3J(H,H) = 7.6, 4 H); 7.95 (*d*, ^3J(H,H) = 7.6, 4 H); 8.32 (*s*, NH_2). Anal. calc. for $C_{21}H_{19}N_3O_3 \cdot 0.5\ H_2O$ (370.41): C 68.10, H 5.44, N 11.34; found: C 67.81, H 5.17, N 11.31.

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