JOC Article

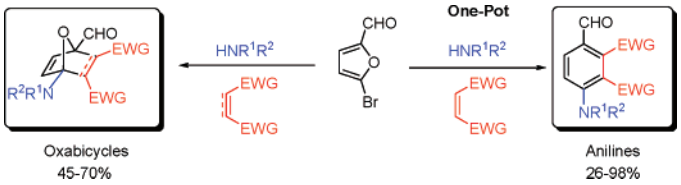
From Furans to Anilines: Toward One-Pot Two-Step Amination/Diels−Alder Sequences

Raouf Medimagh,[†] Sylvain Marque,*[,†] Damien Prim,*[,†] Saber Chatti,[‡] and Hédi Zarrouk[‡]

Institut Lavoisier de Versailles (ILV) UMR CNRS 8180, Université de Versailles-Saint-Quentin-en-Yvelines, 45 Avenue des Etats-Unis, 78 035 Versailles, Cedex, France, and Laboratoire de Chimie Verte, Institut National de Recherche et d'Analyse Physico-chimique (INRAP), Pôle Technologique de Sidi Thabet, 2020 Sidi Thabet, Tunisia

prim@chimie.uvsq.fr; sylvain.marque@chimie.uvsq.fr

Received November 20, 2007



Selective metal-free amination and Diels−Alder reactions are described in the furan series, leading to polysubstituted anilines or to stable oxabicyclic adducts in high yield. Interestingly, anilines are conveniently prepared through a novel one-pot, two-step amination/Diels−Alder procedure from commercially available 5-bromo-2-furaldehyde.

Introduction

The past decades have witnessed the versatility of furan derivatives as building block in total synthesis of natural products and pharmaceuticals.[1,2] Among the most significant examples in the furan chemistry, Diels−Alder cycloadditions using this heterocycle as the 4π diene are of particular interest. This pericyclic process is one of the most employed strategies for the construction of six-membered rings. Although general experimental conditions as temperature, solvent, concentration of substrates obviously influence the reaction course, yields and selectivities are strongly depending on the substitution pattern of the furan ring. An overview of the recent literature clearly sets suitable combinations of substituents at the furan heterocycle and shows the structural diversity of transient or stable adducts obtained through cycloadditions of furans. If furan itself is able to undergo [4 + 2] cycloaddition reactions,[1,3,4] it has been shown that the introduction of both electron-donating groups and/or electron-withdrawing groups at position 2 of the furan enhanced its reactivity[5] and extended the scope of this reaction. Indeed, molecular orbital (MO) and FMO calculations concluded in an increase of HOMO energy levels.[2] For instance, a combination of amino and ester groups led to a clear increase of HOMO energy levels rising from −9.3 eV for furan to −8.8 eV for 5-aminofuran-2-carboxylate methyl ester. The latter breakthrough has been elegantly examplified by Padwa and others in the syntheses of complex polycyclic molecules or advanced intermediates.[2,6−15] Among the latter, 2-aminofurans revealed especially useful partners in the preparation of cyclohexadienes derivatives and polysubstituted anilines through bi-(inter)-molecular processes. In this context, cycloadditions of substituted 2-amino furanes, bearing an additional NO_2 or CN group,

[†] Université de Versailles-Saint-Quentin-en-Yvelines.
[‡] Institut National de Recherche et d'Analyse Physico-chimique (INRAP).

(1) Kappe, O. C.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179−14233.
(2) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088−4096.
(3) Ouellette, R. J.; Rosenblum, A.; Booth, G. *J. Org. Chem.* **1968**, *33*, 4302−4303.
(4) Kienzle, F. *Helv. Chim. Acta* **1975**, *58*, 1180−1183.
(5) Potts, K. T.; Walsh, E. B. *J. Org. Chem.* **1988**, *53*, 1199−1202.
(6) Dean, F. *Adv. Heterocycl. Chem.* **1982**, *31*, 237−334.
(7) Jung, M. E.; Truc, V. C. *Tetrahedron Lett.* **1988**, *29*, 6059−6062.
(8) Schlessinger, R. H.; Bergstorm, C. P. *J. Org. Chem.* **1995**, *60*, 16−17.
(9) Schlessinger, R. H.; Bergstorm, C. P. *Tetrahedron Lett.* **1996**, *37*, 2133−2136.
(10) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304−5305.
(11) Padwa, A.; Kappe, O. C.; Reger, T. S. *J. Org. Chem.* **1996**, *61*, 4888−4889.
(12) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617−4626.
(13) Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609−2617.
(14) Gustafsson, J.; Sterner, O. *J. Org. Chem.* **1994**, *59*, 3994−3997.
(15) Cochran, J. E.; Wu, T.; Padwa, A. *Tetrahedron Lett.* **1996**, *37*, 2903−2906.

10.1021/jo7024916 CCC: $40.75
Published on Web 02/27/2008

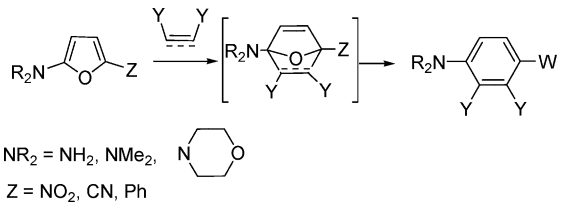


FIGURE 1. Direct access to anilines.

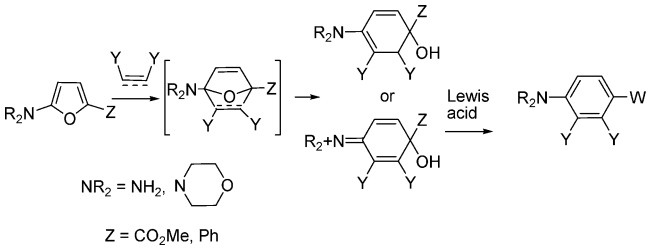


FIGURE 2. Access to cyclohexadienes and anilines.

with various dienophiles allowed direct access to anilines with good overall yields (Figure 1).[2,16,17]

Interestingly, 2-amino furanes, bearing mild electron-withdrawing groups, selectively afforded cyclohexadiene derivatives. In a further step and after Lewis acid treatment, the later may transform into the corresponding anilines or phenols (Figure 2).[15,18]

These Diels−Alder reactions are assumed to proceed through the formation of 7-oxabicyclo[2.2.1] adducts. However, such intermediates are usually not observed. In most cases, rearomatization into the aniline derivatives spontaneously results from either dehydration or a rearrangement of the cycloadduct, even when using DMAD as the dienophile.

Although the Diels−Alder reaction starting from 2-amino furanes offer competitive access to such anilines and/or key intermediates, this strategy suffers from the lack of convenient preparation methods to such reactive heterocycles. The preparation of 2-amino furanes is only scarcely reported and mainly requires several steps such as dinitration of furane and subsequent displacement of one nitro group by an amine,[2] preparation of nitrofuroate followed by Pd-catalyzed reduction,[15] intervention by iron carbene complexes,[16] or cyclopropenone ring opening in the presence of carbonyl metals.[17]

Recently, we reported on the metal-free amination of bromoheterocycles bearing carboxaldehydes, in aqueous medium.[19−21] This procedure allowed the formation of aminoheterocycles, including furanes, in high yields from commercially available starting material. A typical example is depicted in Figure 3.

The ^{1}H NMR spectra of compounds **1** and **2** are noteworthy to observe the influence by the introduction of the amino substituent on the chemical shifts of the residual protons of the furan ring (Figure 3). Indeed, the proton H-3 and H-4 of **1** resonate at $\delta = 7.17$ and 6.54 ppm, respectively. In compound **2**, they resonate at $\delta = 7.08$ and 5.22 ppm, respectively. No significant shielding for H-3 was observed whereas the large shielding $\Delta\delta = -1.32$ observed for H-4 is in good agreement

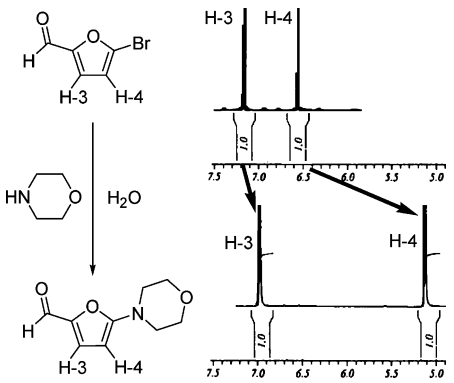


FIGURE 3. Shielding observed for H-3 and H-4 protons of 5-aminofuranes.

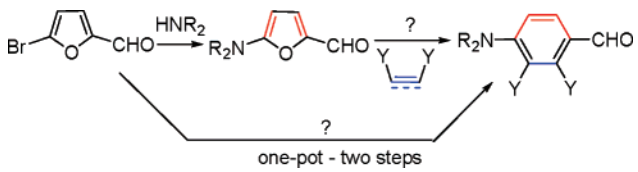
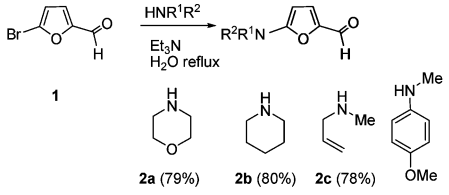


FIGURE 4. From furan to aniline: one-pot, two-step access.

SCHEME 1. Amination of 5-Bromo-2-furaldehyde[d]



Entry	Compound	Time	Yield (%)	H-3	H-4	Δδ (c) H-3 (1-2)	Δδ(c) H-4 (1-2)
1	**2a**	20min	79	7.08	5.22	-0.09	-1.32
2	**2b**	20min	80	7.17	5.25	0	-1.29
3	**2c**[a]	6h	78	7.19	5.16	+0.02	-1.38
4	**2d**[b]	10h	48	7.22	5.23	+0.05	-1.31

[a] Amination was carried out in a mixture of dioxane:water 90:10. [b] Amination was carried out with only 1.1 equiv of amine and 5 equiv of NEt_3. [c] By comparison with proton chemical shifts in 5-bromo-2-furaldehyde (see Figure 3). [d] Reaction conditions: 2:1 equiv of amine and 3 equiv of triethylamine were added to 5-bromofuran-2-carboxaldehyde refluxing in water.

with a decrease of the aromatic character and concomitant increase of the diene character of 2-aminofurans. Thus, we anticipated that this novel amine−carboxaldehyde combination onto a furan ring would be effective as dienic partner in Diels−Alder reactions and would afford new aniline derivatives. In addition, we wondered if a one-pot, two-step amination/cycloaddition sequence starting from bromofuraldehyde would also allow the formation of anilines (Figure 4).

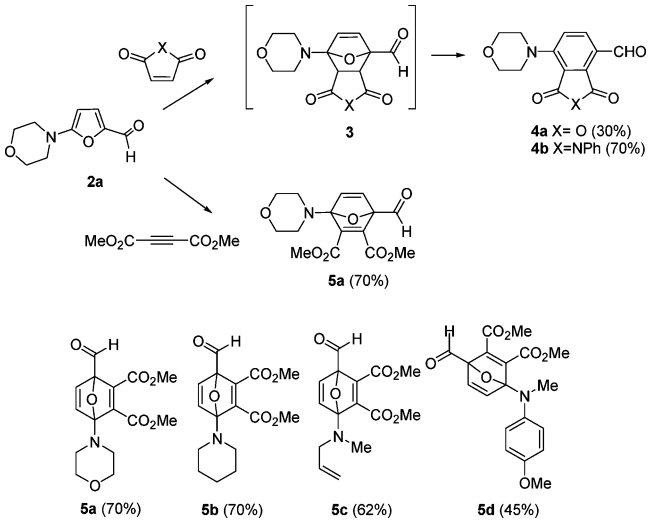
We report herein on the realization of this concept.

Results and Discussion

Amination Reaction. First, we prepared a new set of aminofuraldehydes by metal-free amination in aqueous media.[19] Secondary cyclic, acyclic and aromatic amines were tested and the corresponding targets were isolated in good yields (Scheme 1). In general, the amination reactions were carried out in water using 2 equiv of the reacting amine and an additional 3 equiv of triethylamine.

(16) Semmelhack, M. F.; Park, J. *Organometallics* **1986**, *5*, 2550−2552.
(17) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1987**, *52*, 4408−4409.
(18) Boyd, G. V.; Heatherington, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2523−2531.
(19) Prim, D.; Kirsch, G. *Tetrahedron* **1999**, *55*, 6511−6526.
(20) Prim, D.; Kirsch, G.; Nicoud, J.-F. *Synlett* **1998**, 383−384.
(21) Migianu, E.; Prim, D.; Kirsch, G. *Synlett* **2000**, 459−462.

SCHEME 2. Selective Diels−Alder Reactions



If the amination reaction afforded the morpholino- and piperidino-furan in 79% and 80%, respectively, within 20 min, 6- and 10-h reaction courses were required to ensure completion when using *N*-methylallylamine and *N*-methyl *p*-anisidine (entries 3 and 4). In the latter cases, optimization of reaction conditions and increase of additional base to 5 equiv had no beneficial effect on isolated yields. In addition, attempts to use organic solvents such as toluene or dioxane instead of water led to a decrease of amination rates and are in full agreement with previous data.[19,20] However, the use of dioxane /water mixture revealed beneficial in increasing the solubility of reactants and decreasing amount of side products. Indeed, as already established,[19] the presence of water avoided the formation of an aminal intermediate and thus increased both amination rates and yields.

It is worth noting that proton H-3 and H-4 in compounds **2a**−**d** show similar characteristic chemical shifts (Scheme 1). In all cases, introduction of the amino group only poorly affected the chemical shifts of H-3 in aminofurans **2a**−**d**. In contrast, strong shielding ranging from −1.29 to −1.38 ppm were observed for H-4, indicating a similar influence of the amino substituent on the electronic distribution into the furan diene, regardless of its cyclic, acyclic or aromatic structure.

Diels−Alder Reaction. Having various 5-aminofuraldehydes in hand, we next examined their behavior in Diels−Alder reactions. Cycloadditions were tested with three different dienophiles: *N*-phenylmaleimide, maleic anhydride and dimethylacetylene dicarboxylate (DMAD). To evaluate the dienic potential of furans bearing an original donor−acceptor substituent combination (amine-aldehyde), morpholino furaldehyde **2a** was chosen as the model compound. In a first set of reactions furan **2a** reacted with *N*-phenylmaleimide in water. Disappointingly, poor results or degradation byproducts have been obtained. The same reaction with either *N*-phenylmaleimide or maleic anhydride in toluene or dioxane at 70 °C afforded the expected anilines in 70% and 30% yields, respectively (Scheme 2). Although these cycloadditions are assumed to proceed through the oxabicycles **3**, the latter were not observed. Spontaneous ring opening followed by dehydration accounted for rearomatization and formation of anilines **4a** and **4b**. The modest yield obtained in case of **4a**, was partly attributed to an enhanced sensitivity of the anhydride toward hydrolysis and water.

TABLE 1. Optimization of the One-pot Process[a]

entry	morpholine (equiv)	NEt_3 (equiv)	dienophile (equiv)	time (h)[b]	yield (%)
1	3	4	3	18	25
2	2	2	3	18	54
3	2	2	1	18	26
4	2	2	4	18	79
5	2	2	4	24	98

[a] Reaction conditions: 5-bromofuran-2-carboxaldehyde, morpholine, NEt_3 in refluxing 1,4-dioxane/water 9:1 during 4 h, then $MgSO_4$ followed by *N*-phenylmaleimide. [b] The indicated reaction time refers to the Diels−Alder step.

Moving from *N*-phenylmaleimide and maleic anhydride to DMAD led to unexpected products. In constrast to the literature data we were able to isolate the oxabicycle **5a** in 70% yield. Moreover, the latter exhibit high stability, can be exposed to air, and stored at room temperature without degradation. Gratifyingly, four novel oxabicyclic structures **5a**−**d** could be isolated after cycloadditions using the parent amino furans **2a**−**d** under identical reaction conditions. Plausibly, the less marked donor-attractor system (amine-carboxaldehyde) by comparison with other combination described in the literature[15] (involving ester and nitro groups) may avoid the rearomatization process and keep the oxabridge safe.

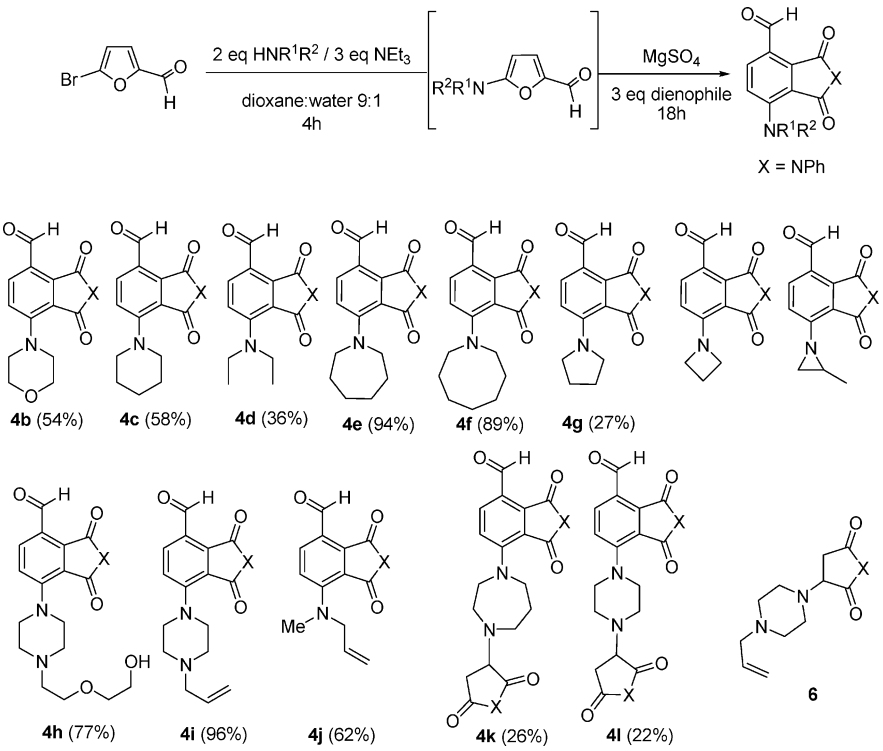
Toward One-Pot Amination/Diels−Alder Process. Encouraged by the results obtained in the above amination and cycloaddition reactions, we started to examine combination of both reactions in a one-pot sequence using **1**, morpholine and *N*-phenylmaleimide as starting material. The major point was to determine suitable conditions for both reactions. If water was the adequate solvent for the amination reaction, the cycloaddition required toluene or dioxane to proceed without side reactions. Thus, due to the high boiling point and water-miscible character, 1,4-dioxane was chosen as common solvent for both reactions.

In a first experiment under one-pot conditions, 3 equiv of morpholine, 4 equiv of triethylamine and 3 equiv of dienophile were reacted with furane **1**. Only traces of aniline **4b** could be detected in ^1H NMR of the crude material in dioxane. Thus, we started optimization of several parameters such as solvent, dienophile/diene and morpholine/triethylamine ratios.

The same reaction was then realized using dioxane/water combination in various ratios and monitored by TLC. Complete disappearance of the starting furan **1** was observed in 4 h using a 9/1 dioxane/water ratio. Subsequent addition of the dienophile led to various results depending on the presence of an additive. Indeed, only the presence of $MgSO_4$ as dehydration agent allowed us to isolate aniline **4b** in 25% yield (Table 1, entry 1). In addition, both morpholine/Et_3N and **2a**/dienophile ratios were essential to the obtention of anilines. As indicated in Table 1, when the reaction was carried out with 2 equiv of morpholine and Et_3N, a substancial increase of aniline yields was observed (entry 2), most likely due to the absence or minimization of nucleophilic addition of residual amines at the dienophile.[22] Moreover, dramatic influence of dienophile amounts over the reaction rates is shown in entries 3 and 4. Reducing the amount of dienophile to 1 equiv led to poor results (entry 3). In contrast, the use of 4 equiv afforded the expected aniline **4b** in a good

(22) In addition to expected anilines, side products rising from Michael addition type of residual secondary amines on the dienophile were also obtained. Data collected are in full agreement with the structure of the side product. See experimental part for a full characterization of the compound **6**.

SCHEME 3. Anilines 4 through One-Pot Process



overall 79% yield (entry 4). Finally, the best result was obtained with 2 equiv of morpholine, 2 equiv of Et_3N, 4 equiv of dienophile and increasing reaction time to 24 h. In these conditions aniline **4b** was isolated in nearly quantitative yield (entry 5).

Next, other amines were checked in the one-pot amination/Diels−Alder sequence (Scheme 3). Gratifyingly, several new anilines, substituted by valuable carbonyl groups, were prepared in overall satisfactory yields according to the aforementioned procedure. The same conditions (Table 1, entry 2) were used to appreciate at best the reactivity of secondary amines and not to hide their nucleophilic features.

Results depicted in Scheme 3 deserve some comments. First, our results corroborate the general nucleophilic reactivity order established in recent Mayr's group calculations.[23] Increase of the nitrogen atom donating ability in the starting amine and aminofuran led to a clear enhancement of both amination and Diels−Alder reactions. Classical synchronous as well as asynchronous Diels−Alder mechanisms may account for the results we observed in these series. It is also worth noting that increase of ring strain from six- to three-membered cyclic amine resulted in a sharp decrease of the amination and/or Diels−Alder efficiency. Indeed, pyrrolidine-based aniline **4g** was isolated with a modest 27% and degradation took place with azetidine and aziridine derivatives. Second, this procedure tolerates functionalized amines as exemplified in structures **4h**−**j**, which were obtained in yields ranging from 62% to 96%. The use of unprotected bis-amines such as piperazine and homopiperazine led to unexpected results. No traces of dimeric compounds resulting from a double amination/Diels−Alder sequence could be isolated. In contrast, the mono amination/Diels−Alder sequence followed by Michael addition between the residual free nitrogen atom and *N*-phenylmaleimide afforded **4k** and **4l** in 22% and 26% yields, respectively. Third, purification of furans, especially when substituted by polar and functionalized amino groups, is a tedious task, due in part to their well-known instability. The one-pot amination/Diels−Alder sequence not only avoids dull purification of the intermediates but also allows a more easy purification of the less polar anilines.

(23) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679−3688.

Conclusion

In conclusion, we have developed a novel amination/Diels−Alder reaction sequence from furans to anilines. This one-pot, two-step procedure allowed the easy preparation of polysubstituted anilines. In addition, we also highlighted the first selective synthesis of stable oxabicyclic structures in Diels−Alder reactions involving aminofuraldehydes as dienophiles.

Experimental Section

General. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. Petroleum ether was distilled under argon. Toluene and 1,4-dioxane were used without distillation. All reactions were carried out under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was purified by silica gel chromatography using an ethyl acetate/petroleum ether mixture as the eluent unless specified otherwise. NMR spectra were recorded on a 300 and 200 MHz Brucker spectrometer. Chemical shifts were reported in ppm relative to the residual solvent peak (7.26 ppm for $CHCl_3$, 2.05 ppm for acetone) for ^1H spectra and (77.00 ppm for $CDCl_3$, 206.00 ppm for acetone-d_6) for ^{13}C spectra. Melting points were measured on a Büchi Melting-Point B-545 and were uncorrected. High-resolution mass spectroscopy data were recorded on a Autospec Ultima (Waters/Micromass) device with a resolution of 5000 RP at 5%. Impact electronic and chemical ionization spectroscopies were recorded on a HP5989 B device of Hewlett-Packard; for electrospray mass

spectroscopy an add-on 59 987 A was used; Branford source-type; 4 μL/min. Infrared spectra were recorded on a FT IR spectrometer Nicolet Impact 400 D of Nicolet Instruments in KBr for liquid and solid compounds. TLC was carried out on Silica Gel 60 F_{254} (0.5 mm thickness).

General Procedure for Amination. In a 25 mL round-bottom flask were mixed 1 g of 5-bromo-2-furaldehyde (5.71 mmol), 2.38 mL of triethylamine (17.13 mmol, 3 equiv) and 1055 μL of morpholine (12 mmol, 2 equiv) in 4 mL of water. The mixture was heated at reflux for 20 min. The medium was allowed to cool down at room temperature then extracted with 3 × 10 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/EtOAc 7:3) to give 818 mg of 5-morpholino-2-furancarboxaldehyde **2a** as brown crystals (79%).[19]

5-Piperidino-2-furancarboxaldehyde 2b. Following the general procedure for amination, 5-bromo-2-furaldehyde led to brown crystals (80%) after flash chromatography (petroleum ether/EtOAc 7:3).[19]

5-(*N*-Allyl-*N*-methyl)amino-2-furancarboxaldehyde 2c. Following the general procedure for amination, 5-bromo-2-furaldehyde led to a purple oil (78%) after flash chromatography (petroleum ether/EtOAc 6:4). IR (KBr, ν, cm^{-1}): 3125.6, 3080.9, 2932.6, 2808.2, 1650.3, 1584.8, 1542.3, 1423.1, 1403.2, 1334.5, 1300.3, 1036.5, 1008.5, 919.8, 890.6, 775.6. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.01 (s, 3H, NCH_3), 3.96 (d, ^3J = 5.7 Hz, 2H, NCH_2CHCH_2), 5.16−5.24 (m, 3H, NCH_2CHCH_2 + HC═CN), 5.68−5.88 (m, 1H, NCH_2CHCH_2), 7.19 (d, ^3J = 3.3 Hz, 1H, *H*C═CCHO), 8.95 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.3 (NCH_3), 52.9 ($NCH_2CH═CH_2$), 86.2 (HC═$CNMeCH_2CHCH_2$), 118.0 ($NCH_2CH═CH_2$), 131.5 ($NCH_2CH═CH_2$), 131.7 (C, HC═$CNMeCH_2CHCH_2$), 144.0 (HC═CCHO), 163.3 (C, HC═CCHO), 170.5 (CHO). HR-MS *m*/*z* calcd for $C_9H_{11}NO_2$ 165.0790, found 165.0791 ± 0.0001

5-(4-*N*-Methoxyphenyl-*N*-methylamino)-2-furancarboxaldehyde 2d. Following the general procedure for amination, 5-bromo-2-furaldehyde led to a yellow solid (48%) after flash chromatography (petroleum ether/EtOAc 65:35). Mp 70.1−70.8 °C. IR (KBr, ν, cm^{-1}): 3138.9, 2914.1, 2821.0, 1646.1, 1589.7, 1563.6, 1536.4, 1506.7, 1401.7, 1342.5, 1303.5, 1240.3, 1167.8, 1026.5, 752.3, 720.5, 560.7, 529.9. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.44 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 5.22 (d, ^3J = 3.8 Hz, 1H, HC═CN), 6.90 (d, ^3J = 8.9 Hz, 2H, Ph), 7.19−7.26 (m, 3H, Ph + HC═CCHO), 9.02 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.7 (NCH_3), 55.5 (OCH_3), 88.4 (HC═$CNPhOCH_3$), 114.8 (CH, NC═*C*H−HC═COMe), 125.9 (CH, NC═CH−HC═COMe), 131.2 (HC═CCHO), 136.6 (C, HC═$CNPhOCH_3$), 144.5 (C), 157.9 (C, HC═*C*CHO), 162.9 (C), 171.1 (CHO). CI-MS NH_3 *m*/*z* (rel int): 463 (10, 2M + H^+), 249 (1, M + NH_4^+), 232 (100, MH^+).

General Procedure for Cycloaddition. A mixture of 50 mg of amino furaldehyde (0.27 mmol) and 0.81 mmol (3 equiv) of dienophile was stirred in toluene (2 mL) and heated at 70 °C for 18 h. The solution was concentrated at reduced pressure, and then the residue was purified.

Following the procedure for cycloaddition, 50 mg of **2a** (0.27 mmol) and 140.3 mg of *N*-phenylmaleimide (0.81 mmol, 3 equiv) were mixed in toluene. After reaction, then concentration in vaccum, the crude was purified by silica gel chromatography (petroleum ether/EtOAc 1:1) to afford aniline **4b** as yellow crystals (79%). Mp 232.4−233.6 °C. TLC: R_f = 0.31 (cyclohexane/EtOAc 6:4). IR (KBr, ν, cm^{-1}): 2969.3, 2867.8, 1707.0, 1685.6, 1610.4, 1495.2, 1400.6, 1381.5, 1242.3, 1201.5, 1165.3, 1117.3, 992.9, 762.5, 692.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.51 (t, ^3J = 4.6 Hz, 4H, NCH_2), 3.93 (t, ^3J = 4.6 Hz, 4H, OCH_2) 7.21 (d, ^3J = 13.2 Hz, ^5J = 0.7 Hz, 1H, HC═CN), 7.39−7.42 (m, 3H, Ph), 7.48−7.54 (m, 2H, Ph), 8.17 (d, ^3J = 13.2 Hz, 1H, *H*C═CCHO), 10.96 (d, ^5J = 0.7 Hz, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.4 (2C, NCH_2), 66.7 (2C, OCH_2), 116.0 (C), 122.3 (HC═CN), 126.1 (C), 126.9 (2CH), 128.4 (CH), 129.2 (2CH), 131.2 (C), 133.5 (HC═CCHO), 135.2 (C), 153.1 (C), 166.1 (CON), 166.7 (CON), 188.2 (CHO). EI-MS *m*/*z* (rel int): 336 (20), 318 (40), 306 (35), 293 (45), 250 (25), 167 (40), 149 (80), 57 (100). ESI-MS MeOH *m*/*z* (rel int): 695.3 (15, 2M + Na^+), 393.5 (50), 391.3 (55, M + MeOH + Na^+), 367.3 (20), 359.3 (100). HR-MS *m*/*z* calcd for $C_{19}H_{16}N_2O_4$ 336.1110, found 336.1110 ± 0.0001.

Aniline 4a. Following the procedure of cycloaddition, 50 mg of **2a** (0.27 mmol) and 79.4 mg of maleic anhydride (0.81 mmol, 3 equiv) were mixed in toluene. After reaction, then concentration in vaccum, the crude was purified by silica gel chromatography (petroleum ether/EtOAc 7:3) to give a yellow solid (30%). Mp 187.5−189 °C. IR (KBr, ν, cm^{-1}): 2963.0, 2925.6, 2852.4, 1827.3, 1766.1, 1684.0, 1671.9, 1616.9, 1547.8, 1435.9, 1261.4, 1240.0, 1214.8, 1111.7, 1052.8, 1019.7, 984.9, 918.6, 901.7, 801.4, 747.9. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.56−3.59 (m, 4H, NCH_2), 3.93−3.96 (m, 4H, OCH_2), 7.23 (d, ^3J = 9.1 Hz, 1H, HC═CN), 8.22 (d, 1H, ^3J = 8.9 Hz, *H*C═CCHO), 10.78 (s, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 51.5 (2C, NCH_2), 66.9 (2C, OCH_2), 115.7 (C), 123.8 (HC═CN), 126.0 (C), 134.5 (HC═CCHO), 135.9 (C), 154.2 (C), 165.8 (COO), 166.6 (COO), 186.7 (CHO). ESI-MS MeOH *m*/*z* (rel int): 316.2 (15, M + MeOH + Na^+), 338.2 (10, M + MeONa + Na^+). HR-MS *m*/*z* calcd for $C_{13}H_{11}NO_5$ 261.0637, found 261.0637 ± 0.0001.

Cycloadduct 5a. Following the procedure of cycloaddition, 50 mg of **2a** (0.27 mmol) and 100 μL of dimethylacethylene dicarboxylate (0.81 mmol, 3 equiv) were mixed in toluene. After reaction, then concentration in vaccum, the crude was purified by extraction with cold petroleum ether. The combined organic phase was concentrated under reduced pressure and afforded the pure cycloadduct (70%). Mp 198.2−199.5 °C. IR (KBr, ν, cm^{-1}): 2979.2, 2958.5, 2860.6, 2830.3, 1735.5, 1683.3, 1583.2, 1474.5, 1441.2, 1340.1, 1318.9, 1248.9, 1187.2, 1150.8, 1112.8, 984.8, 864.9, 728.5. ^{1}H NMR (acetone-d_6, 300 MHz): δ 2.81−2.85 (m, 4H, NCH_2), 3.64−3.67 (m, 4H, OCH_2), 3.87 (s, 3H, CO_2Me), 3.92 (s, 3H, CO_2Me), 7.06 (d, ^3J = 9.1 Hz, 1H, HC−CN), 7.61 (d, ^3J = 8.9 Hz, 1H, *H*C−CCHO), 10.75 (s, 1H, CHO). ^{13}C NMR (acetone-d_6, 75 MHz): δ 52.2 (NC−CCO_2CH_3), 53.2 (HOCC−CCO_2CH_3), 54.1 (2C, NCH_2), 67.8 (2C, OCH_2), 110.1 (C), 119.9 (HC−CN), 131.1 (HC−CCHO), 135.7 (C), 143.1 (C, C═C), 159.5 (C, C═C), 168.3 (NC−CCO_2CH_3), 169.7 (HOCC−CCO_2CH_3), 190.5 (CHO). HR-MS *m*/*z* calcd for $C_{15}H_{17}NO_7$ 323.1005, found 323.1005 ± 0.0001.

Cycloadduct 5b. Following the procedure of cycloaddition, 50 mg of **2b** (0.27 mmol) and 100 μL of dimethylacethylene dicarboxylate (0.81 mmol, 3 equiv) led to a brown oil (70%). Mp 61.8−63.8 °C. IR (KBr, ν, cm^{-1}): 2918.5, 2849.1, 1740.2, 1727.8, 1679.8, 1466.4, 1441.7, 1335.9, 1242.2, 1212.1, 1015.2. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1.50−1.59 (m, 6H, $NCH_2CH_2CH_2$), 2.76−2.86 (m, 4H, NCH_2), 3.85 (s, 3H, CO_2Me), 3.92 (s, 3H, CO_2Me), 7.02 (d, ^3J = 8.9 Hz, 1H, HC−CN), 7.55 (d, ^3J = 9.1 Hz, 1H, *H*C−CCHO), 10.72 (s, 1H, CHO). ^{13}C NMR (acetone-d_6, 75 MHz): δ 24.6 ($NCH_2CH_2CH_2$), 27.3 (2C, $NCH_2CH_2CH_2$), 52.1 (NC−CCO_2CH_3), 53.1 (HOCC−CCO_2CH_3), 55.2 (2C, NCH_2), 109.9 (C), 119.8 (HC−CN), 131.2 (HC−CCHO), 135.5 (C), 144.7 (NCC═C), 159.3 (OHCCC═C), 168.4 (NC−CCO_2CH_3), 169.9 (HOCC−CCO_2CH_3), 190.4 (CHO). CI-MS CH_4 *m*/*z* (rel int): 294 (100, (M − CO)H^+), 322 (42, MH^+). HR-MS *m*/*z* calcd for $C_{16}H_{19}NO_6$ 321.1212, found 321.1218 ± 0.0001.

Cycloadduct 5c. Following the procedure of cycloaddition, 50 mg of **2c** (0.27 mmol) and 100 μL of dimethylacethylene dicarboxylate (0.81 mmol, 3 equiv) afforded a colorless solid (62%). IR (KBr, ν, cm^{-1}): 3129.1, 2931.3, 2808.6, 1650.1, 1585.8, 1542.7, 1403.7, 1334.3, 1300.8, 1036.7, 1008.5, 775.6. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.57 (s, 3H, NMe), 3.40 (d, ^3J = 6.2 Hz, 2H, NCH_2CHCH_2), 3.88 (s, 3H, CO_2Me), 3.90 (s, 3H, CO_2Me), 5.04−5.16 (m, 2H, NCH_2CHCH_2), 5.68−5.82 (m, 1H, NCH_2CHCH_2), 7.01 (d, ^3J = 9 Hz, 1H, HC−CN), 7.40 (d, ^3J = 9.1 Hz, 1H, *H*C−CCHO), 10.90 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.0

(NCH_3), 52.2 (NC−CCO_2CH_3), 52.9 (HOCC−CCO_2CH_3), 61.0 ($NCH_2CH{=}CH_2$), 108.8 (C), 117.1 ($NCH_2CH{=}CH_2$), 119.5 (HC−CN), 131.0 (HC−CCHO), 134.2 (C), 135.4 ($NCH_2CH{=}CH_2$), 142.8 (C, C=C), 159.1 (C, C=C), 168.6 (NC−CCO_2CH_3), 169.2 (HOCC−CCO_2CH_3), 188.9 (CHO). ESI-MS CH_3CN *m/z* (rel int): 280.2 (100, $(M - CO)H^+$), 302.2 (60, $(M + Na^+) - CO$), 330.2 (50, $M + Na^+$), 346.2 (20, $M + K^+$), 581.4 (30, $2(M - CO) + Na^+$), 637.1 (10, $2M + Na^+$). HR-MS *m/z* calcd for $C_{15}H_{17}NO_6$ 307.1056, found 307.1056 ± 0.0001.

Cycloadduct 5d. Following the procedure of cycloaddition, 50 mg of **2d** (0.27 mmol) and 100 μL of dimethylacethylene dicarboxylate (0.81 mmol, 3 equiv) afforded a solid (45%). IR (KBr, ν, cm^{-1}): 3141.1, 3004.6, 2951.4, 2928.5, 1728.1, 1681.5, 1512.0, 1444.7, 1323.4, 1241.9, 1203.2, 1035.4, 1013.2, 818.9, 804.2. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.07 (s, 3H, NCH_3), 3.75 (m, 6H, OCH_3+ CO_2Me), 3.94 (s, 3H, CO_2Me), 6.59 (d, $^3J = 9.2$ Hz, 1H, Ph), 6.76 (d, $^3J = 9.2$ Hz, 1H, Ph), 7.06 (d, $^3J = 8.9$ Hz, 2H, HC−CN), 7.25−7.27 (m, 2H, Ph + *H*C−CCHO), 11.06 (d, $^4J = 0.4$ Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 41.1 (NCH_3), 52.3 (NC−CCO_2CH_3), 53.4 (HOCC−CCO_2CH_3), 55.6 (OCH_3), 110.7 (C), 114.8 (2C, NC*C*H=CHCOMe), 116.9 (2C, NCCH=*C*HCOMe), 117.6 (C), 121.3 (H*C*−CNPhOMe), 137.1 (H*C*−CCHO), 140.6 (C), 145.1 (HC−*C*NPhOMe), 153.7 (*C*CHO), 160.5 (C), 168.0 (NC−CCO_2CH_3), 169.7 (HOCC−CCO_2CH_3), 190.9 (CHO). ESI-MS CH_3CN *m/z* (rel int): 368.2 (80, $(M + Na^+) - CO$), 384.2 (100, $(M + K^+) - CO$), 412.1 (25, $M + K^+$), 713.3 (70, $2(M - CO) + Na^+$). HR-MS *m/z* calcd for $C_{19}H_{19}NO_7$ 373.1162, found 373.1161 ± 0.0001.

General Procedure for One-Pot Process. In a 25 mL round-bottom flask was dissolved 63.7 mg of 5-bromo-2-furaldehyde (0.35 mmol) in 2.0 mL of 1,4-dioxane and 0.2 mL of water. 0.07 mL of morpholine (0.78 mmol, 2 equiv) and 0.10 mL of triethylamine (0.72 mmol, 2 equiv) were added then the resulting solution was stirred with an oversized magnetic bar during 4 h at reflux. The mixture was allowed to cool down at room temperature, then 2 g of magnesium sulfate were added, and 253.7 mg of *N*-phenylmaleimide (1.43 mmol, 4 equiv). The mixture was refluxed for 24 h, then the medium was allowed to cool down at room temperature and the solvent was removed under vaccum. The residue purified by flash-chromatography with a gradient of cyclohexane/EtOAc 70:30 to 60:40 as eluent led to 116.6 mg of rearomatized cycloadduct **4b** (0.347 mmol, 98%) as yellow crystals.

Other rearomatized cycloadducts (**4c**-**4l**) were obtained by this one-pot procedure with 2 equiv of secondary amine, 2 equiv of triethylamine, 3 equiv of *N*-phenylmaleimide. The reaction time was always of 4 h for the amination step, then 18 h for the Diels−Alder.

Aniline Piperidine 4c. Yellow crystals, 58% yield, mp 198.2−199.5 °C. TLC: $R_f = 0.72$ (cyclohexane/EtOAc 6:4), 0.21 (cyclohexane/EtOAc 9:1). IR (KBr, ν, cm^{-1}): 2928.4, 2848.9, 1705.0, 1684.6, 1610.3, 1502.1, 1378.4, 1242.9, 1186.1, 1129.0, 1114.2, 761.6, 690.4. ^1H NMR (300 MHz, $CDCl_3$): δ 1.65−1.72 (m, 2H, $NCH_2CH_2CH_2$), 1.77−1.84 (m, 4H, NCH_2CH_2), 3.49 (t, $^3J = 5.3$ Hz, 4H, NCH_2), 7.20 (d, $^3J = 8.9$ Hz, 1H, HC=CN), 7.39−7.43 (m, 3H, Ph), 7.48−7.54 (m, 2H, Ph), 8.11 (d, $^3J = 9.1$ Hz, 1H, *H*C=CCHO), 10.95 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.8 ($NCH_2CH_2CH_2$), 25.90 (2C, NCH_2CH_2), 52.6 (2C, NCH_2), 114.9 (C), 122.5 (H*C*=CN), 125.0 (C), 126.9 (2CH), 128.2 (CH), 129.1 (2CH), 131.5 (C), 133.0 (HC=CCHO), 135.5 (C), 153.5 (C), 166.1 (CON), 166.9 (CON), 188.3 (CHO). EI-MS *m/z* (rel int): 334 (100), 305 (45), 277 (50), 250 (45), 241 (25), 213 (25), 185 (25), 167 (25), 158 (25), 84 (50), 77 (50). CI-MS NH_3 *m/z* (rel int): 335 (100, MH^+). HR-MS *m/z* calcd for $C_{20}H_{18}N_2O_3$ 334.1317, found 334.1318 ± 0.0001.

Aniline Diethylamine 4d. Yellow oil, 36% yield. TLC: $R_f =$ 0.53 (petroleum ether/EtOAc 8:2). IR (KBr, ν, cm^{-1}): 2970.4, 2931.0, 2875.8, 1696.4, 1675.8, 1610.0, 1543.8, 1504.2, 1424.6, 1404.4, 1396.6, 1258.6, 1153.9, 741.3, 694.3. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, $^3J = 7.0$ Hz, 6H, NCH_2CH_3), 3.66 (t, $^3J = 7.1$ Hz, 4H, NCH_2), 7.12 (dd, $^3J = 9.2$ Hz, $^5J = 0.8$ Hz, 1H, HC=CN), 7.24−7.46 (m, 5H, Ph), 8.00 (dd, $^3J = 9.1$ Hz, $^4J = 1.1$ Hz, 1H, *H*C=CCHO), 10.89 (d, $^5J = 0.8$ Hz, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0 (2C, NCH_2CH_3), 46.9 (2C, NCH_2), 112.5 (C), 121.6 (H*C*=CN), 124.0 (C), 127.0 (2CH), 128.2 (CH), 129.1 (2CH), 131.6 (C), 132.5 (HC=CCHO), 136.2 (C), 151.4 (C), 166.4 (CON), 166.9 (CON), 188.5 (CHO), EI-MS *m/z* (rel int): 322 (60), 307 (45), 293 (100), 279 (25), 265 (10), 249 (15), 77 (20). CI-MS NH_3 *m/z* (rel int): 323 (100, MH^+).

Aniline Homopiperidine 4e. Yellow crystals, 94% yield, mp 160.4−161.5 °C. TLC: $R_f = 0.13$ (cyclohexane/EtOAc 9:1). IR (KBr, ν, cm^{-1}): 2944.6, 2929.2, 2852.8, 1701.3, 1671.4, 1611.5, 1539.9, 1504.9, 1423.2, 1378.4, 1257.1, 1162.2, 765.5. ^1H NMR (300 MHz, $CDCl_3$): δ 1.59−1.63 (m, 4H, $NCH_2CH_2CH_2$), 1.86−1.90 (m, 4H, NCH_2CH_2), 3.80 (t, $^3J = 5.8$ Hz, 4H, NCH_2), 7.15 (d, $^3J = 9.2$ Hz, 1H, HC=CN), 7.40−7.48 (m, 3H, Ph), 7.50−7.54 (m, 2H, Ph), 8.05 (d, $^3J = 9.2$ Hz, 1H, *H*C=CCHO), 10.96 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.5 (2C, $NCH_2CH_2CH_2$), 28.0 (2C, NCH_2CH_2), 53.5 (2C, NCH_2), 110.8 (C), 120.8 (H*C*=CN), 123.5 (C), 127.0 (2CH), 128.2 (CH), 129.1 (2CH), 131.6 (C), 132.1 (HC=CCHO), 136.4 (C), 152.0 (C), 166.4 (CON), 167.0 (CON), 188.5 (CHO). EI-MS *m/z* (rel int): 348 (100), 305 (80), 277 (50), 255 (25). CI-MS CH_4 *m/z* (rel int): 389 (10, $MC_3H_5^+$), 377 (25, $MC_2H_5^+$), 349 (100, MH^+). ESI-MS *m/z* (rel int): 719.4 (50, $2M + Na^+$), 371.3 (100, $M + Na^+$). HR-MS *m/z* calcd for $C_{21}H_{20}N_2O_3$ 348.1473, found 348.1475 ± 0.0001.

Aniline (Dihomo)piperidine 4f. Yellow crystals, 89% yield, mp 117.7−122.9 °C. TLC: $R_f = 0.30$ (cyclohexane/EtOAc 9:1). IR (KBr, ν, cm^{-1}): 2952.5, 2929.0, 2852.7, 1754.9, 1705.7, 1669.4, 1611.2, 1534.6, 1517.5, 1500.9, 1455.5, 1425.1, 1381.7, 1343.7, 1268.9, 1209.2, 1173.9, 1118.6, 820.9, 762.3, 749.6, 691.9. ^1H NMR (300 MHz, $CDCl_3$): δ 1.40−1.65 (m, 6H, $NCH_2CH_2CH_2CH_2CH_2$), 1.72−1.83 (m, 4H, NCH_2CH_2), 3.82 (t, $^3J = 5.9$ Hz, 4H, NCH_2), 7.05 (d, $^3J = 9.4$ Hz, 1H, HC=CN), 7.30−7.36 (m, 3H, Ph), 7.39−7.46 (m, 2H, Ph), 7.98 (d, $^3J = 9.3$ Hz, 1H, *H*C=CCHO), 10.90 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5 (2C, $NCH_2CH_2CH_2$), 26.6 (CH_2), 26.4 (2C, NCH_2CH_2), 54.2 (2C, NCH_2), 110.6 (C), 120.8 (H*C*=CN), 123.5 (C), 127.2 (2CH), 128.3 (CH), 129.2 (2CH), 131.7 (C), 132.4 (HC=CCHO), 136.6 (C), 150.9 (C), 166.5 (CON), 167.0 (CON), 188.6 (CHO). ESI-MS *m/z* (rel int): 385.3 (20, $M + Na^+$), 287.3 (100). HR-MS *m/z* calcd for $C_{22}H_{22}N_2O_3$ 362.1630, found 362.1630 ± 0.0001.

Aniline Pyrollidine 4g. Yellow crystals, 27% yield, mp 224.4−225.5 °C. TLC: $R_f = 0.60$ (cyclohexane/EtOAc 6:4), 0.29 (petroleum ether/EtOAc 8:2). IR (KBr, ν, cm^{-1}): 2962.3, 2922.1, 2874.0, 1702.1, 1680.6, 1612.3, 1545.5, 1503.4, 1427.3, 1376.8, 1361.3, 1254.9, 1196.7, 1155.4, 1116.2, 763.4, 689.5, 624.4. ^1H NMR (300 MHz, $CDCl_3$): δ 2.01−2.06 (m, 4H, NCH_2CH_2), 3.73 (t, $^3J = 6.5$ Hz, 4H, NCH_2) 6.96 (d, $^3J = 9.2$ Hz, 1H, HC=CN), 7.37−7.42 (m, 3H, Ph), 7.48−7.53 (m, 2H, Ph), 8.04 (d, $^3J = 8.7$ Hz, 1H, *H*C=CCHO), 10.94 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (2C, NCH_2CH_2), 52.4 (2C, NCH_2), 110.0 (C), 119.8 (H*C*=CN), 123.1 (C), 126.9 (2CH), 128.1 (CH), 129.0 (2CH), 131.6 (C), 132.3 (HC=CCHO), 136.0 (C), 149.1 (C), 166.4 (CON), 167.0 (CON), 188.4 (CHO). EI-MS *m/z* (rel int): 320 (100), 291 (40), 264 (40), 263(40), 235 (50), 223 (20), 160 (25), 144 (20), 77 (25). CI-MS NH_3 *m/z* (rel int): 321 (100, MH^+). HR-MS *m/z* calcd for $C_{19}H_{16}N_2O_3$ 320.1161, found 320.1160 ± 0.0001.

Aniline Hydroxyethoxypiperazine 4h. Yellow oil, 77% yield. TLC: $R_f = 0.14$ (EtOAc: MeOH 9:1). IR (KBr, ν, cm^{-1}): 3369.3, 2945.2, 2828.1, 1731.5, 1707.9, 1610.5, 1499.7, 1454.8, 1379.9, 1296.9, 1237.6, 1139.5. ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (t, $^3J = 5.3$ Hz, 2H, NCH_2), 2.70−2.80 (m, 4H, NCH_2), 3.50−3.55 (m, 4H, OCH_2), 3.60−3.63 (m, 2H, OCH_2), 3.67−3.70 (m, 4H, OCH_2), 3.79 (br, 1H, OH), 7.17 (d, $^3J = 8.9$ Hz, 1H, NCH), 7.37−7.41 (m, 3H, Ph), 7.47−7.50 (m, 2H, Ph), 8.11 (dd, $^3J = 8.9$ Hz, $^4J = 1.7$ Hz, 1H, *H*C=CCHO), 10.92 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7 ($2NCH_2$), 53.0 ($2NCH_2$), 57.6 (OCH_2), 61.8 (OCH_2), 67.4 (OCH_2), 72.3 (OCH_2), 115.7 (C), 122.5 (H*C*=CN),

125.7 (C), 126.8 (2CH), 128.3 (CH), 129.1 (2CH), 131.2 (C), 133.3 (H*C*═CCHO), 135.1 (C), 152.9 (C), 166.0 (CON), 166.7 (CON), 188.1 (CHO). EI-MS *m*/*z* (rel int): 423 (10), 380 (25), 349 (30), 348 (100), 305 (20). CI-MS CH_4 *m*/*z* (rel int): 452 (15, $MC_2H_5^+$), 424 (100, MH^+), 348 (15). ESI-MS, MeOH *m*/*z* (rel int): 478.2 (95, M + MeOH + Na^+), 456.2 (75, M + $MeOH^+$), 446.1 (100, M + Na^+), 424.1 (50, MH^+). HR-MS *m*/*z* calcd for $C_{23}H_{25}N_3O_5$ 423.1794, found 423.1793 ± 0.0001.

Aniline Allylpiperazine 4i. Yellow crystals, 91% yield, mp 97.3−98.8 °C. IR (KBr, ν, cm^{-1}): 3069.4, 2874.1, 2815.1, 1764.2, 1710.6, 1680.7, 1609.5, 1552.9, 1501.0, 1445.4, 1382.2, 1336.0, 1237.2, 1196.5, 1173.8, 1119.0, 1004.2, 921.1, 762.2, 747.6, 691.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (t, ^3J = 4.7 Hz, 4H, NCH_2), 2.98 (d, ^3J = 6.5 Hz, 4H, NCH_2CHCH_2), 3.47 (t, ^3J = 4.7 Hz, 4H, NCH_2), 5.08−5.17 (m, 2H, NCH_2CHCH_2), 5.72−5.85 (m, 1H, NCH_2CHCH_2), 7.10 (d, ^3J = 9.1 Hz, 1H, HC═CN), 7.29−7.34 (m, 3H, Ph), 7.39−7.44 (m, 2H, Ph), 8.03 (d, ^3J = 8.9 Hz, 1H, *H*C═CCHO), 10.85 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.9 (2C, NCH_2), 52.6 (2C, NCH_2), 61.3 (NCH_2CHCH_2), 115.3 (C), 118.6 (NCH_2CHCH_2), 122.4 (H*C*═CN), 125.5 (C), 126.8 (2CH), 128.2 (CH), 128.9 (CH), 129.0 (CH), 131.2 (C), 133.2 (NCH_2CHCH_2), 134.2 (H*C*═CCHO), 135.1 (C), 152.9 (C), 165.9 (CON), 166.7 (CON), 188.0 (CHO). EI-MS *m*/*z* (rel int): 375 (20), 334 (10), 306 (20), 279 (15), 96 (100). CI-MS NH_3 *m*/*z* (rel int): 376 (100, MH^+). ESI-MS, MeOH *m*/*z* (rel int): 537.4 (25), 451.3 (50), 441.4 (30), 430.3 (60, M + MeOH + Na^+), 408.4 (100, M + MeOH + H^+), 398.3 (100, M + Na^+), 376.4 (100, MH^+). HR-MS *m*/*z* calcd for $C_{22}H_{21}N_3O_3$ 375.1583, found 375.1583 ± 0.0001.

Aniline *N*-Methylallylamine 4j. Yellow solid, 62% yield, mp 75.2−80.2 °C. TLC: R_f = 0.78 (pentane/EtOAc 6:4). IR (KBr, ν, cm^{-1}): 3070.3, 2964.7, 2874.1, 1747.8, 1705.3, 1680.4, 1609.9, 1550.3, 1502.8, 1402.5, 1374.6, 1248.2, 1200.3, 1174.1, 1143.0, 1115.9, 917.1, 826.6, 764.1, 691.8, 624.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.06 (s, 3H, NMe), 4.05 (d, ^3J = 5.6 Hz, 2H, NCH_2CHCH_2), 5.08−5.21 (m, 2H, NCH_2CHCH_2), 5.81−5.94 (m, 1H, NCH_2CHCH_2), 7.02 (d, ^3J = 9.1 Hz, 1H, HC═CN), 7.11−7.45 (m, 5H, Ph), 7.96 (d, ^3J = 9.1 Hz, 1H, *H*C═CCHO), 10.85 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.3 (NCH_3), 58.2 (NCH_2CHCH_2), 118.4 (NCH_2CHCH_2), 121.6 (H*C*═CN), 124.2 (C), 125.9 (CH), 126.8 (CH), 127.8 (CH), 128.1 (CH), 129.0 (2CH), 132.4 (C), 132.8 (NCH_2CHCH_2), 134.0 (H*C*═CCHO), 135.6 (C), 152.4 (C), 166.0 (CON), 166.8 (CON), 188.1 (CHO). ESI-MS, MeOH *m*/*z* (rel int): 375.2 (25, M + MeOH + Na^+), 359.4 (15, M + K^+), 343.2 (100, M + Na^+). HR-MS *m*/*z* calcd for $C_{19}H_{16}N_2O_3$ 320.1161, found 320.1160 ± 0.0001.

Aniline Homopiperazine 4k. Yellow solid, 26% yield, mp 116.4−119.4 °C. TLC: R_f = 0.22 (cyclohexane/EtOAc 3:7). IR (KBr, ν, cm^{-1}): 2928.7, 2852.0, 1709.0, 1671.9, 1609.2, 1543.9, 1499.7, 1455.5, 1419.0, 1379.3, 1194.0, 1165.9, 1119.4, 1070.2, 762.5, 694.0. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09−2.11 (m, 2H, $NCH_2CH_2CH_2N$), 2.72 (dd, ^2J = 18.7 Hz, ^3J = 5.2 Hz, 1H, H_2CCON), 2.78−2.90 (m, 1H, H_2CCON), 3.01−3.13 (m, 3H, $NCH_2CH_2CH_2N$+ NCH_2CH_2N), 3.19−3.26 (m, 1H, NCH_2CH_2N), 3.80 (t, ^3J = 5.7 Hz, 2H, $NCH_2CH_2CH_2N$), 3.93 (t, ^3J = 4.5 Hz, 1H, NCH_2CH_2N), 4.08 (dd, ^3J = 9.2 Hz, ^3J = 5.1 Hz, 1H, NCH), 7.14 (d, ^3J = 9.2 Hz, 1H, HC═CN), 7.23−7.25 (m, 1H, Ph), 7.38−7.54 (m, 9H, Ph), 8.07 (d, ^3J = 9.2 Hz, 1H, *H*C═CCHO), 10.96 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4 ($NCH_2CH_2CH_2N$), 32.8 (CH_2CON), 52.0 (NCH_2), 52.1 (NCH_2), 52.9 (NCH_2), 54.4 (NCH_2), 63.6 (*C*HCON), 117.7 (C), 120.8 (H*C*═CN), 124.1 (C), 126.3 (2CH), 127.0 (2CH), 128.2 (CH), 128.8 (CH), 129.1 (4CH), 131.3 (C), 131.4 (C), 132.5 (H*C*═CCHO), 136.0 (C), 152.0 (C), 166.3 (CON), 166.8 (CON), 173.8 (CON), 175.3 (CON), 188.3 (CHO). EI-MS *m*/*z* (rel int): 522 (5), 448 (20), 434 (25), 402 (20), 205 (25), 173 (80), 146 (40), 119 (35), 113 (50), 103 (35), 93 (100). CI-MS CH_4 *m*/*z* (rel int): 523 (2, MH^+), 350 (25), 206 (100), 174 (95). ESI-MS, MeOH *m*/*z* (rel int): 1099.8 (10, 2M + MeOH + Na^+), 1067.6 (15, 2M + Na^+), 598.3 (40), 591.4 (60), 577.4 (60, M + MeOH + Na^+), 545.3 (100, M + Na^+), 413.3 (30). HR-MS *m*/*z* calcd for $C_{30}H_{26}N_4O_5$ 522.1903, found 522.1901 ± 0.0001.

Aniline Piperazine 4l. Yellow oil, 22% yield. TLC: R_f = 0.13 (cyclohexane/EtOAc 4:6). IR (KBr, ν, cm^{-1}): 2925.1, 2850.9, 1711.5, 1609.8, 1499.9, 1444.0, 1382.3, 1240.5, 1172.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78−2.86 (m, 2H, NCH_2+H_2CCON), 2.92−2.99 (m, 1H, H_2CCON), 3.05−3.08 (m, 2H, NCH_2), 3.52−3.95 (m, 4H, NCH_2), 3.97−4.00 (m, 1H, NCH), 7.14 (d, ^3J = 8.9 Hz, 1H, HC═CN), 7.19−7.21 (m, 2H, Ph), 7.32−7.48 (m, 8H, Ph), 8.10 (dd, ^3J = 8.9 Hz, ^4J = 1.5 Hz, 1H, *H*C═CCHO), 10.90 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.3 (CH_2CON), 49.1 (2C, NCH_2), 51.1 (2C, NCH_2), 62.4 (*C*HCON), 115.9 (C), 122.6 (H*C*═CN), 126.0 (C), 126.4 (2CH), 126.9 (2CH), 128.4 (CH), 128.8 (CH), 129.2 (4CH), 131.2 (C), 131.3 (C), 133.5 (H*C*═CCHO), 135.2 (C), 152.8 (C), 166.1 (CON), 166.7 (CON), 173.7 (CON), 174.6 (CON), 188.2 (CHO). EI-MS *m*/*z* (rel int): 508 (40), 334 (25), 305 (50), 293 (30), 229 (100), 173 (75), 119 (50). CI-MS CH_4 *m*/*z* (rel int): 524 (50), 391 (50), 279 (30), 261 (60), 206 (75), 183 (100). ESI-MS, MeOH *m*/*z* (rel int): 584.3 (40), 577.4 (50), 563.3 (75, M + MeOH + Na^+), 531.2 (100, M + Na^+), 413.3 (25), 172.1 (80). HR-MS *m*/*z* calcd for $C_{29}H_{24}N_4O_5$ 508.1747, found 508.1743 ± 0.0001.

Michael Allylpiperazine 6. Yellow oil. IR (KBr, ν, cm^{-1}): 3076.6, 2943.0, 2810.3, 1708.1, 1609.8, 1499.3, 1455.9, 1390.0, 1375.3, 1296.4, 1203.9, 1161.1, 1130.9, 1008.1, 758.3, 705.8, 697.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (m, 3H), 2.56−2.64 (m, 3H), 2.80−2.96 (m, 6H), 3.88 (dd, ^3J = 8.7 Hz, ^3J = 5.1 Hz, 1H, *H*CCONPh), 5.08−5.16 (m, 2H, NCH_2CHCH_2), 5.71−5.85 (m, 1H, NCH_2CHCH_2), 7.17−7.20 (m, 2H, Ph), 7.31−7.42 (m, 3H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.4 ($H_2CCONPh$), 48.9 (NCH_2CH_2N), 52.7 (2C, NCH_2CH_2N), 61.4 (NCH_2CHCH_2), 62.3 (*C*HCONPh), 118.3 (NCH_2CHCH_2), 126.4 (2CH), 128.6 (CH), 129.1 (2CH), 131.4 (C), 134.5 (NCH_2CHCH_2), 174.0 (CON), 174.8 (CON). EI-MS *m*/*z* (rel int): 299 (15), 272 (20), 211 (100), 170 (30), 125 (50). CI-MS NH_3 *m*/*z* (rel int): 300 (100, MH^+). ESI-MS *m*/*z* (rel int): 322.4 (30, M + Na^+), 300.3 (100, MH^+). HR-MS *m*/*z* calcd for $C_{17}H_{21}N_3O_2$ 299.1634, found 299.1633 ± 0.0001.

Acknowledgment. The authors are grateful to CNRS for a grant (R.M.) and to the Université de Versailles-Saint-Quentin-en-Yvelines for financial and material support. The authors have highly appreciated the helpful discussions with Vincent Steinmeltz (ILV) in the mass spectrocopy elucidation of several structures. We are also grateful to Dr. Sami Barrek & Chaouki Belgacem (INRAP) for the high-resolution mass spectrospy determinations.

Supporting Information Available: ^{1}H and ^{13}C NMR spectral characterization data for compounds **2c**, **2d**, **4a**−**l**, **5a**−**d**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7024916