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Toward versatile methods leading to highly functionalized imidazo[1,2-*a*]pyridines

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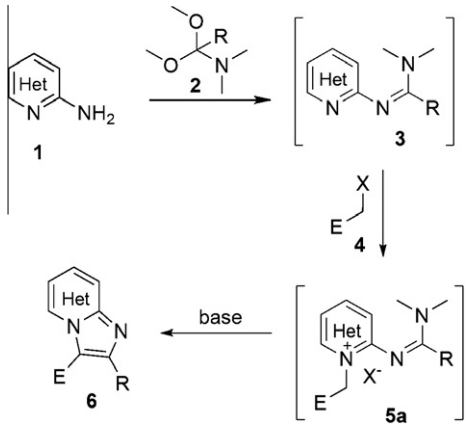
ABSTRACT

A convenient and general method of preparation of polyfunctionalized imidazo[1,2-*a*]pyridines is reported. This methodology involves activation of secondary amides leading to the formation of the corresponding amidines **9**. Different activating reagents have been evaluated and the efficiency of PCl_5 was illustrated with alkyl functionalized groups.

Introduction

Imidazo[1,2-*a*]pyridines are an important class of molecules due to their wide spectrum of biological activities and clinical applications.[1] Their core ring system is present in numerous antiviral,[2] antiprotozoal[3] and antiherpes[4] drugs. Several procedures have been developed for the synthesis of imidazo[1,2-*a*]pyridines,[5] but only a few studies leading to chemical diversity on the imidazole ring are reported.[6] More recently we decided to re-investigate a chemical approach earlier described by Tisler and co-workers[7] and briefly depicted in Scheme 1. Treatment of the 2-amino-aza-heterocycle **1** with ketal **2** gave amidines **3**. These key intermediates treated with the α-bromo-carbonylmethyl reagent **4** yielded ammonium salt **5a** which, under basic conditions, afforded the final imidazo azines **6** bearing an electron-withdrawing group in position 3 (E = COMe, COPh). However, only few amide ketals **2** are commercially available (R = H or Me), or are difficult to prepare.

The main objective of this communication deals with alternative approaches leading to amidines **3** in order to diversify the substituent R. Pyridine was chosen as the reference system leading to amidines **9** (Scheme 2). Two strategies could be formally followed for their preparation. Both started from amides, a secondary amide **7** in pathway a, and a tertiary amide **10** in pathway b, and are involved in an activation step leading in each case to electrophilic intermediates (compounds **8** and **11**, respectively).



Scheme 1. General route for preparation of disubstituted imidazo[1,2-*a*]azines. R = H, Me; E = COMe, COPh; Het = heterocycle.

Amination using either secondary amines or 2-aminopyridine gave the expected amidines **9**.

We explored the different known methods for amide activation, in particular chlorinating agents ($POCl_3$,[8] $SOCl_2$,[9] PCl_5,[10] $(COCl)_2$,[11]) tosyl chloride[12] or triflic anhydride,[13] or catalysts such as Lewis acid catalysts ($TiCl_4$,[14] $SiCl_4$[15]) and also BtH.[16]

Based on literature data including our previous work[14–16] on structurally related amide systems, selected activating reagents were used with either the secondary amide **7** (Scheme 3, Table 1) or the tertiary amide **10** (Table 2).

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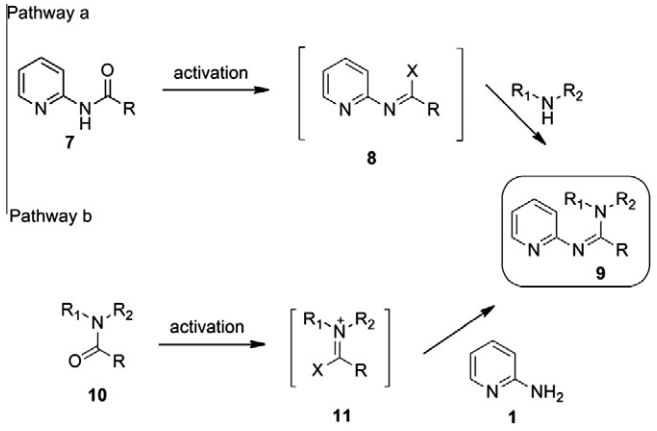
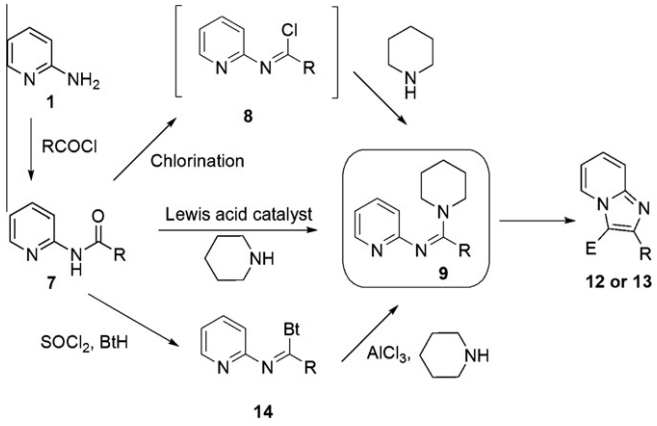


Scheme 2. Alternative pathways leading to the amidine intermediates **9** R ≠ H, Me.



Scheme 3. Different pathways leading to the key intermediates **9**.

The *N*-acyl-2-pyridinamines **7** were prepared by careful monoacylation of 2-aminopyridine **1**. To avoid risks of N,N-diacylation with acylchlorides, the reaction was performed in pyridine at 60 °C for aryl, or heteroaryl carboxylic acids, or in dichloromethane at −78 °C for aliphatic carboxylic acids. However, the N,N-diacylated amines could be easily converted into N-monoacylated derivatives **7** by treatment in basic medium.[17]

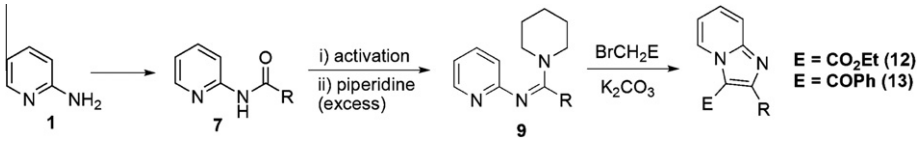
N-Pyridin-2-ylpentanamide **7a** was used for analysis of the scope and limitations of different activating agents (Table 1, entry 1). Efficacy of the activation step can be directly illustrated by the cumulative yield formation of imidazopyridines **12** (E = CO_2Et) or **13** (COPh), since intermediate **9** was reacted with α-halomethylketones or esters in basic medium without any purification. Results are summarized in Table 1.

Among the different chlorinating agents, only PCl_5 gave satisfactory results, whereas, thionyl chloride or phosphorous oxytrichloride failed under our experimental conditions (entries 3 and 4). Considering different Lewis acid catalysts, good yields could be obtained with titanium tetrachloride, whereas, the use of $SiCl_4$,[15,16] a milder Lewis acid catalyst, failed. $TiCl_4$[14] was already used with success in our laboratory to turn cyclic secondary amides into the corresponding tertiary amidines.

Amides **7** bearing different functional groups were used to evaluate the scope of the amidine **9** synthesis. The use of $TiCl_4$ could be generalized to various derivatives including aryl (entries 7–11), heteroaryl (**7g**) and benzyl (**7b**, **c**).[19] However, the reaction failed when using alkyl functionalized groups such as $-(CH_2)_2CO_2Et$, $-(CH_2)_2NHZ$ or $-(CH_2)_3N_3$ (entries 14, 16 and 17), probably as the result of important hydrolysis. Nevertheless, when using PCl_5, the expected imidazopyridines **12j, k**, **13i**, were efficiently obtained without significant hydrolysis.[20] Spectral (MS ^1H and ^{13}C NMR) properties of **12** and **13** were consistent with the imidazopyridine structure.[7] In particular **12** and **13** exhibited a characteristic downfield shift δ 9.4 ± 0.15 of the imidazo[1,2-*a*]pyridine H-5.[23]

In the case of **7h** (entry 13) two unexpected compounds (**17** and **21**) were obtained instead of **13h**, and characterized. They most

Table 1
Preparation of imidazo[1,2-*a*]pyridines **12** and **13** by activation of secondary amides



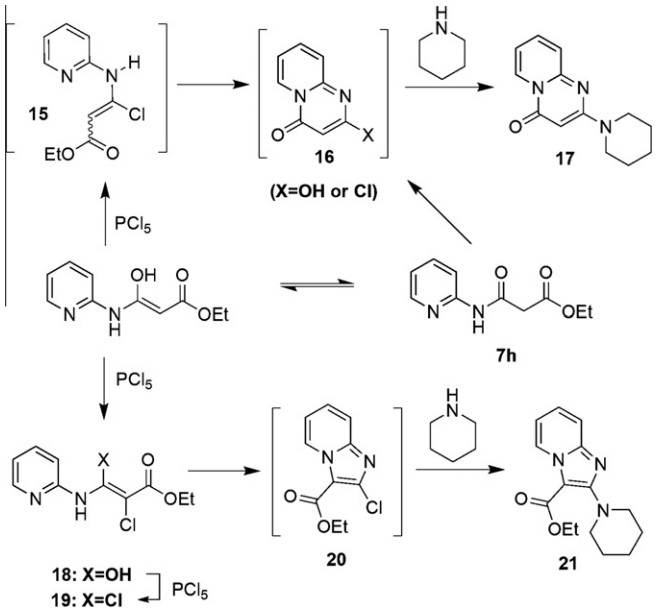
Entry	*R*	*N*°	Yield **7** (%)	Activation	*E*	*N*°	Cumulative yield[a] **7**–**12**, **13** (%)
1	Butyl	**7a**	67	$TiCl_4$	COPh	**13a**	88
2				PCl_5			65
3				$POCl_3$			nr
4				$SOCl_2$			nr
5	Bn	**7b**	83	$TiCl_4$	CO_2Et	**12b**	66
6	4-Cl-Bn	**7c**	72	$TiCl_4$	CO_2Et	**12c**	69
7	4-Cl-Ph	**7d**	92	$TiCl_4$	COPh	**13d**	72
8					CO_2Et	**12d**	80
9	3,4$(OMe)_2$-Ph	**7e**	83	$TiCl_4$	COPh	**13e**	73
10					CO_2Et	**12e**	97
11	4-CN-Ph	**7f**	82	$TiCl_4$	CO_2Et	**12f**	65
12	3-Pyridyl	**7g**	70	$TiCl_4$	COPh	**13g**	62
13	CH_2CO_2Et	**7h**	63	PCl_5	—	**13h**	0
14	$(CH_2)_2CO_2Et$	**7i**	50	$TiCl_4$	COPh	**13i**	0
15				PCl_5	COPh	**13i**	63
16	$(CH_2)_2NHCbz$	**7j**	63	PCl_5	CO_2Et	**12j**	37[a,b]
17	$(CH_2)_3N_3$	**7k**	75	PCl_5	CO_2Et	**12k**	61

nr: no reaction in our experimental conditions.
[a] Yield based on recovered compound after purification.
[b] Yield not optimized.

Table 2
Preparation of imidazo[1,2-*a*]pyridines **12**, **13** by activation of tertiary amides **10**

Entry	*R*	NR_1R_2	Activation	*E*	*N*°	Yield[a] (%)
1	*n*-Bu	Piperidine	$TiCl_4$	COPh	**13a**	88
2	$(CH_2)_3N_3$	Piperidine	$TiCl_4$	CO_2Et	**12k**	0
3	Me	$N(Me)_2$	$TiCl_4$	CO_2Et	**12l**	91
4	$(CH_2)_2Ph$	Piperidine	$TiCl_4$	COPh	**13m**	82
5	$(CH_2)_2Ph$	Piperidine	Tf_2O	COPh	**13m**	25
6	$(CH_2)_2Ph$	Piperidine	PCl_5	COPh	**13m**	25

[a] Yield based on recovered compound after purification.



Scheme 4. Reactivity of **7h** with PCl_5.

probably resulted from the existence of a prototropic system proposed in Scheme 4.

The enamino ester of **7h** may be first chlorinated affording the free rotating intermediate **15**, which easily cyclized into the bicyclic pyrimido pyridine **16**. Nevertheless, direct cyclization of **7h** into the enol **16** (X = OH) could not be discarded. A final treatment with excess of piperidine provided a new stable compound **17** in a satisfactory overall yield (45%). However, in the presence of excess of PCl_5, a second chlorination may occur and might lead successively to intermediate **18** (X = OH) and **19** (X = Cl), which may cyclize into another bicyclic compound **20**. In the presence of a large excess of piperidine, imidazo[1,2-*a*]pyridine **21** could be recovered as the minor product (30% of the reaction mixture). Chlorination taking place at the acidic methylene group of **7h** is quite surprising, since halogenation of enolic compounds including β-dicarbonyl systems most generally involves bromine, or *N*-bromo or *N*-chlorosuccinimide,[18] or chlorine.

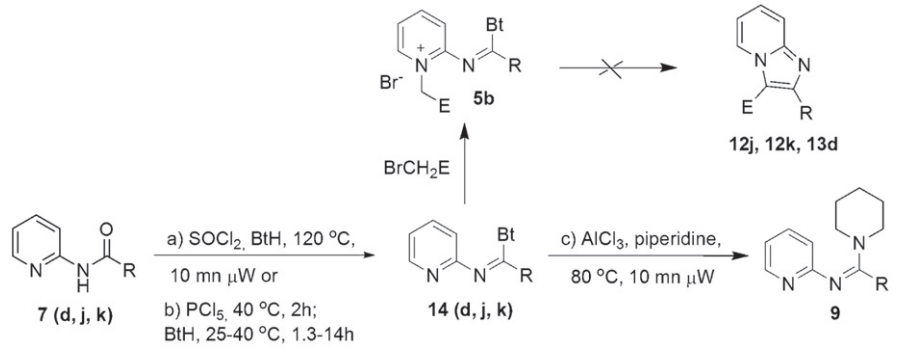
Other strategies were also explored. First, we used the benzotriazole (Bt) intermediate **14** as a stable equivalent of iminochloride **8** (Scheme 5). It could be prepared in a one step reaction combining at first $SOCl_2$ (**14d**) or PCl_5 (**14j**, **k**) activation of the corresponding *N*-acylamidine **7**(**d**, **j**, **k**) in the presence of BtH. However, after alkylation with α-halomethylketone, the pyridinum intermediate **5b** did not cyclize into the final imidazopyridine compounds **12**(**j**, **k**) and **13d**. This lack of reactivity probably results from a lesser leaving group quality of Bt. Nevertheless, the Bt derivative **14** constitutes a stable intermediate, which can be isolated and rapidly activated by means of piperidine in the presence of $AlCl_3$, resulting amidines **9** in good yields.

Reactivity of iminochloride **22** obtained by treatment of **7d** with $SOCl_2$ was also investigated (Scheme 6). When **7d** was involved in a reaction with phenacyl bromide in DMF, the formation of the expected 2-phenyl-3-benzoyl imidazopyridine **13d** was not observed. A first decomposition of **7d** probably took place leading to the starting 2-aminopyridine **1**. It is most likely that the classical Vilsmeier–Haack reaction occurred and the corresponding 3-benzoyl derivative **23** could be isolated in 57% yield. The replacement of DMF by acetonitrile supported our hypothesis, since **13d** was isolated in 30% yield, with still 50% of the starting amide **7d**.

Other activating agents such as oxalyl chloride failed and N-instead of O-acylation was observed with tosyl chloride (compound **24**).

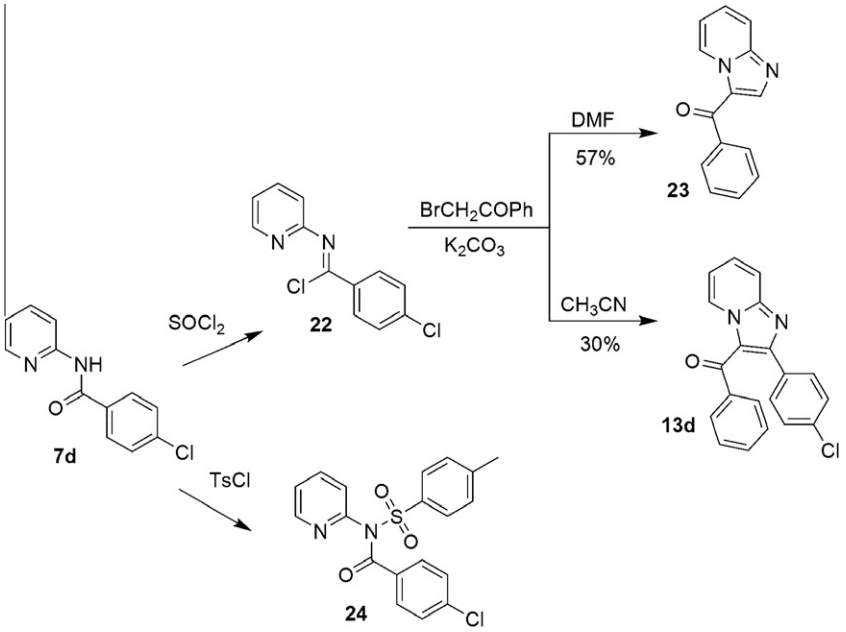
All these reagents have been also evaluated with the second approach involving a starting tertiary amide **10**. Results are given in Table 2.

As observed previously with **7**, $TiCl_4$ is a powerful reagent for the activation of stable tertiary amides with no functional groups (entries 1, 3 and 4). In opposition, the efficiency of PCl_5 was very low, as we obtained only 25% of conversion, when compared to

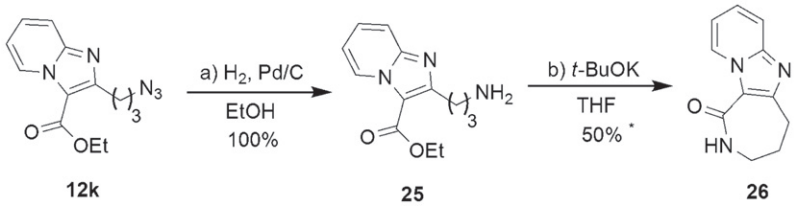


Entry	R	7	14 %	9 %
1	4-Cl-Ph	d	74	100
2	$(CH_2)_2NHZ$	j	49	76
3	$(CH_2)_3N_3$	k	48	99

Scheme 5. Activation with BtH.



Scheme 6. Activation and reactivity of *N*-pyridinyl-benzamide **7d**.

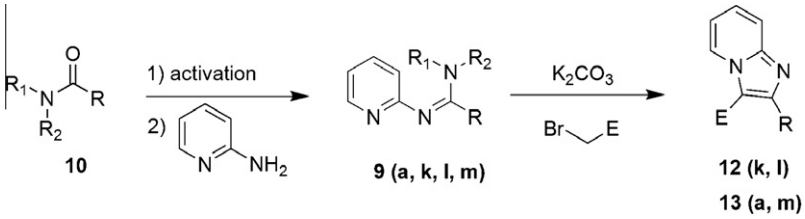


Scheme 7. Access to tetrahydropyrido-imidazo-azepine-1-one.

65% obtained by activation of **7a** (compare entry 6, Table 2 with entry 2, Table 1).

Activation by means of Tf_2O did not improve the yield (only 25% of conversion by means of at least 3 equiv of 2-aminopyridine). This difficulty to activate the tertiary amide is in accordance with previously works described in the literature. For example, an efficient method of preparation of formamidines from primary amines including aminoheterocycles has been described by activation of *N*,*N*-dimethylformamide with sulfonylchloride.[12] However, only limited success was achieved in the synthesis of amidines ($R \neq H$) by this strategy. Other works have used $POCl_3$ for the activation of *N*-acetylpyrolidine, but the corresponding iminochloride was obtained in only 16% yield.[21]

We have described a simple, convenient and efficient preparation of polyfunctionalized imidazo[1,2-*a*]pyridines from amidines **9** resulting from the activation of secondary amides with $TiCl_4$ or PCl_5 in the presence of fragile functional groups. The straightforwardness, the simplicity of the procedure, the mildness of the reaction conditions and the good yields represent significant improvement, when compared with published methods. The reaction is versatile and could yield original 2-functionalized 3-acyl-imidazo[1,2-*a*]pyridines, including compatibility with a variety of functional groups, which may serve for building additional ring systems. Finally, the method presented here allows the preparation of novel scaffolds of great interest for both combinatorial and medicinal chemistry.



Finally, starting from imidazopyridine **12k**, this work allowed us to prepare a tricyclic compound presenting a new scaffold, the tetrahydropyrido-imidazo-azepine-1-one **26**, using a two step sequence involving hydrogenation followed by cyclization of the resulting amine in the presence of *t*-BuOK[22,23] (Scheme 7).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.117.

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19. Representative example of activation of secondary amide **7** with $TiCl_4$.
Preparation of ethyl 2-(3,4-dimethoxyphenyl) imidazo[1,2-a]pyridine-3-carboxylate **12e**. $TiCl_4$ (1 M in toluene, 1.35 mL, 1.35 mmol, 1.2 equiv) was added dropwise to a solution of piperidine (554 μL, 5.61 mmol, 5 equiv) in dioxane (5 mL) under argon. The resulting solution was then heated at 50 °C and 3,4-dimethoxy-*N*-pyridin-2-ylbenzamide **7e** in dioxane (8 mL) was then added dropwise. The final solution was stirred at reflux for 15 h. After evaporation of the volatile, the crude residue was dissolved in ethyl acetate (40 mL). The solution was washed successively with an aqueous saturated $NaHCO_3$ solution (2 × 15 mL) and water (2 × 15 mL). The organic phase was then dried (Na_2SO_4) and evaporated under reduced pressure to give **9**. The resulting product was directly submitted to cyclization. A suspension of **9** (0.20 mmol), the corresponding bromo compound (0.25 mmol) and K_2CO_3 (0.20 mmol) in DMF (2 mL) was heated at 140 °C for 3 h. The reaction mixture was then concentrated under reduced pressure, the residue was dissolved in ethyl acetate (30 mL), washed with water (2 × 10 mL). The organic phase was dried (Na_2SO_4), concentrated to dryness under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford **12e** as a white solid (97%). mp 102–104 °C TLC R_f = 0.52(AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, 3H, J = 7.3 Hz, CH_3), 3.95 (s, 6H, OCH_3), 4.29 (q, 2H, J = 7.3 Hz, OCH_2), 6.90–7.07 (m, 2H, ArH), 7.37–7.49 (m, 3H, ArH), 7.74 (d, 1H, J = 9.0 Hz, ArH), 9.39 (d, 1H, J = 6.8 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.6, 56.3, 60.8, 110.6, 112.1, 113.7, 114.4, 117.7, 123.7, 127.4, 128.3, 128.7, 147.4, 148.5, 150.0, 153.9, 161.6. ESMS *m*/*z*: 327.2 (M+H).
20. Representative example of activation of secondary amide **7** with PCl_5.
Preparation of ethyl 2-(3-azidopropyl)imidazo[1,2-a]pyridine-3-carboxylate **12k**. PCl_5 (1.3 mmol) was added to a solution of *N*-pyridin-2-yl-4-(azido)butanamide **7k** (1.4 mmol) in anhydrous DCM (13 mL). The resulting reaction mixture was stirred at 40 °C under argon for 1.6 h and then the solvent and volatiles were removed under reduced pressure at 27 °C. The crude residue was re-dissolved in anhydrous DCM (13 mL), piperidine (13 mmol) was added in one portion and the final solution was stirred at room temperature until TLC showed complete consumption of starting material (40 mn). The solvent was evaporated under vacuum, the residue taken into diethylether (30 mL), and washed with water (1 × 15 mL), brine (1 × 15 mL). The organic layer was dried (Na_2SO_4) filtered and concentrated under reduced pressure to give *N*-(4-azido-1-(piperidin-1-yl)butylidene)pyridin-2-amine **9k**.
A suspension of **9k** (1 mmol), the corresponding bromo compound (1.5 mmol) and K_2CO_3 (1.5 mmol) in anhydrous DMF (7 mL) was heated at 130 °C until TLC showed complete consumption of starting material (15 h). The reaction mixture was then concentrated under reduced pressure, the residue was dissolved in ethyl acetate (35 mL) and washed with water (2 × 15 mL). The organic phase was dried (Na_2SO_4), concentrated to dryness under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford **12k** as a clear oil (61%) TLC R_f = 0.58 (AcOEt/hept 3:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ:1.38 (t, 3H, J = 7.2 Hz, CH_3), 2.04 (quintet, 2H, J = 6.8 Hz, 7.6 Hz, CH_2-β), 3.14 (t, 2H, J = 7.6 Hz, CH_2-α), 3.32 (t, 2H, J = 6.8 Hz, CH_2-γ), 4.38 (q, 2H, J = 7.2 Hz, OCH_2), 6.91–9.94 (m, 1H, ArH), 7.31–7.35 (m, 1H, ArH), 7.57 (d, 1H, J = 8.8 Hz, ArH), 9.26 (d, 1H, J = 6.8 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 27.3, 28.4, 51.2, 60.5, 113.9, 116.9, 127.8, 128.2. ESMS *m*/*z*: 274.2 (M+H).
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23. Supplementary data available: Experimental procedures and spectral data for compounds **7**, **12**, **13**, **14**, **17**, **21**, **25**, **26**. This material is available free of charge.