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Direct Metalation of Heteroaromatic Esters and Nitriles Using a Mixed Lithium−Cadmium Base. Subsequent Conversion to Dipyridopyrimidinones

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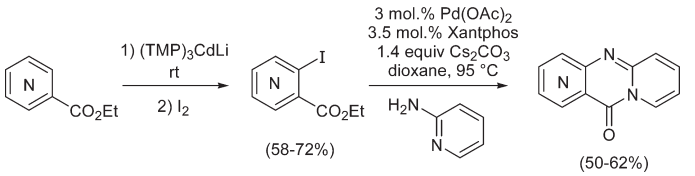
Received November 7, 2009



All pyridine nitriles and esters were metalated at the position next to the directing group using $(TMP)_3CdLi$ in tetrahydrofuran at room temperature. The 2-, 3-, and 4-cyanopyridines were treated with 0.5 equiv of base for 2 h to afford, after subsequent trapping with iodine, the corresponding 3-iodo, 2-iodo, and 3-iodo derivatives, respectively, in yields ranging from 30 to 61%. Cyanopyrazine was similarly functionalized at the 3 position in 43% yield. Ethyl 3-iodopicolinate and -isonicotinate were synthesized from the corresponding pyridine esters in 58 and 65% yield. Less stable ethyl 4-iodonicotinate also formed under the same conditions and was directly converted to ethyl 4-(pyrazol-1-yl)nicotinate in a two-step 38% yield. All three ethyl iodopyridinecarboxylates were involved in a one-pot palladium-catalyzed cross-coupling reaction/cyclization using 2-aminopyridine to afford new dipyrido[1,2-*a*:3′,2′-*d*]pyrimidin-11-one, dipyrido[1,2-*a*:4′,3′-*d*]pyrimidin-11-one, and dipyrido[1,2-*a*:3′,4′-*d*]pyrimidin-5-one in yields ranging from 50 to 62%. A similar cross-coupling/cyclization sequence was applied to methyl 2-chloronicotinate using 2-aminopyridine, 2-amino-5-methylpyridine, and 1-aminoisoquinoline to give the corresponding tricyclic or tetracyclic compounds in 43−79% yield. Dipyrido[1,2-*a*:4′,3′-*d*]pyrimidin-11-one and dipyrido[1,2-*a*:3′,4′-*d*]pyrimidin-5-one showed a good bactericidal activity against *Pseudomonas aeroginosa*. Dipyrido-[1,2-*a*:2′,3′-*d*]pyrimidin-5-one and pyrido[2′,3′:4,5]pyrimidino[2,1-*a*]isoquinolin-8-one showed a fungicidal activity against *Fusarium* and dipyrido[1,2-*a*:4′,3′-*d*]pyrimidin-11-one against *Candida albicans*. Ethyl 4-(pyrazol-1-yl)nicotinate and dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one have promising cytotoxic activities, the former toward a liver carcinoma cell line (HEPG2) and the latter toward a human breast carcinoma cell line (MCF7).

Introduction

Interest in pyridine natural products and pharmaceuticals, as well as pyridine building blocks for various applications such as material science, has resulted in extensive efforts on synthesis methodologies.[1] The deprotonative metalation

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(1) (a) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*, 1st ed.; Pergamon: New York, 1985. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 6.

DOI: 10.1021/jo902385h Published on Web 12/23/2009

using lithium bases has been widely used as a powerful method for the regioselective functionalization of such substrates.[2] Nevertheless, the incompatibility of lithium compounds with reactive functions or sensitive heterocycles can be a limit to their use for the elaboration of complex molecules. Recourse to softer magnesium bases can improve the chemoselectivity of deprotonation reactions, but it is to the detriment of their efficiency since a large excess of base has, in general, to be used.[3]

The use of metal additives to get more efficient or more chemoselective bases (synergic superbases) has been, respectively, developed by Schlosser[4] and Lochmann[5] with LICKOR, mixture of butyllithium (LIC) and potassium *tert*-butoxide (KOR), and by Caubère,[6] Gros and Fort[7] in the pyridine series with BuLi-LiDMAE (DMAE = 2-dimethylaminoethoxide). More recently, other $(R)_n(R')_{n'}MLi$-type bases, but with M different from an alkali metal, have been described by different groups.[8] By combining alkali additives with soft organometallic compounds, bases such as R_2Zn-(TMP)Li(·TMEDA) (R = ^{t}Bu, Bu; TMP = 2,2,6,6-tetramethylpiperidino) (described by the groups of Kondo, Uchiyama, Mulvey, and Hevia),[9] $(TMP)_2Zn·2MgCl_2·2LiCl$[10] and TMPZnCl·LiCl[11] (Knochel), ^{i}Bu$_3$Al(TMP)Li (Uchiyama and Mulvey),[12] Al(TMP)$_3$·3LiCl (Knochel),[13] $(Me_3SiCH_2)_2$-Mn(TMP)Li·TMEDA (Mulvey),[14] and MeCu(TMP)(CN)-Li_2 (Uchiyama and Wheatley)[15] have been prepared, characterized, and used to generate functionalized aromatic compounds.

We recently accomplished the room temperature deprotometalation of a large range of substrates including sensitive heterocycles and functionalized benzenes using a newly developed lithium−cadmium base, $(TMP)_3CdLi$, prepared from $CdCl_2$·TMEDA and 3 equiv of LiTMP.[16] If TMEDA is often employed in solvents of low or modest polarities to enhance the reactivity of a base[9d,e] or to obtain a specific regioselectivity,[2] it was here rather used in order to simplify the reaction protocol, $CdCl_2$·TMEDA being much less sensitive to hydration than free $CdCl_2$.[17]

We here describe the use of $(TMP)_3CdLi$ for the functionalization of pyridine esters and nitriles. Ethyl iodopyridinecarboxylates thus obtained appeared as useful key synthetic intermediates for the synthesis of polycyclic compounds containing a dipyridopyrimidinone skeleton. Some compounds were evaluated for their antimicrobial and cytotoxic activity.

Results and Discussion

Synthetic Aspects. Due to their electrophilic functional group and to their ring prone to nucleophilic attacks, cyanopyridines have never been metalated at room temperature. Reactions using cyano as a group to direct ortho-lithiation have been reported in the benzene series from 1982,[18] but the first example in the pyridine series only appeared 20 years later. Larock and co-workers showed in 2002 that it was possible to lithiate 3-cyanopyridine using LiTMP in tetrahydrofuran (THF) at −78 °C. This result was evidenced by subsequent trapping with iodine to afford a 1:1 mixture of the 2- and 4-iodo compounds in a 50% total yield.[19] Rault and co-workers achieved in 2005 the regioselective[20] functionalization of the other cyanopyridine isomers using 2 equiv of the same hindered lithium amide in THF at −80 °C for 0.75 h.[21]

(2) (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187–304. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090. (c) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489–4505. (d) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161–1172. (e) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595–609.

(3) (a) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414–8416. (b) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Liebigs Ann. Chem.* **1995**, 1441–1446. (c) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Synthesis* **1995**, 1225–1227.

(4) Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627–1634.

(5) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, *7*, 1115–1126.

(6) Caubère, P. *Chem. Rev.* **1993**, *93*, 2317–2334.

(7) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375–3383.

(8) For reviews, see: (a) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060–1075. (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802–3824. (c) Mulvey, R. E. *Acc. Chem. Res.* **2009**, *42*, 743–755.

(9) (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539–3540. (b) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514–8515. (c) Barley, H. R. L.; Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 6018–6021. (d) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2370–2374. (e) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2374–2377. (f) Clegg, W.; Dale, S. H.; Drummond, A. M.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2006**, *128*, 7434–7435. (g) Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kajihara, Y.; Miyoshi, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am. Chem. Soc.* **2008**, *130*, 472–480. (h) Clegg, W.; Conway, B.; Hevia, E.; McCall, M. D.; Russo, L.; Mulvey, R. E. *J. Am. Chem. Soc.* **2009**, *131*, 2375–2384.

(10) (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685–7688. (b) Wunderlich, S.; Knochel, P. *Chem. Commun.* **2008**, 6387–6389. (c) Wunderlich, S. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705–4707. (d) Mosrin, M.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 1468–1477.

(11) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837–1840.

(12) (a) Uchiyama, M.; Naka, H.; Matsumoto, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, *126*, 10526–10527. (b) Garcia-Alvarez, J.; Graham, D. V.; Kennedy, A. R.; Mulvey, R. E.; Weatherstone, S. *Chem. Commun.* **2006**, *30*, 3208–3210. (c) Garcia-Alvarez, J.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E. *Chem. Commun.* **2007**, 2402–2404. (d) Conway, B.; Hevia, E.; García-Álvarez, J.; Graham, D. V.; Kennedy, A. R.; Mulvey, R. E. *Chem. Commun.* **2007**, 5241–5243. (e) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatley, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921–1930. (f) Naka, H.; Morey, J. V.; Haywood, J.; Eisler, D. J.; McPartlin, M.; Garcia, F.; Kudo, H.; Kondo, Y.; Uchiyama, M.; Wheatley, A. E. H. *J. Am. Chem. Soc.* **2008**, *130*, 16193–16200.

(13) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1501–1504.

(14) Garcia-Álvarez, J.; Kennedy, A. R.; Klett, J.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 1105–1108.

(15) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102–15103.

(16) (a) L'Helgoual'ch, J.-M.; Bentabed-Ababsa, G.; Chevallier, F.; Yonehara, M.; Uchiyama, M.; Derdour, A.; Mongin, F. *Chem. Commun.* **2008**, 5375–5377. (b) L'Helgoual'ch, J.-M.; Bentabed-Ababsa, G.; Chevallier, F.; Derdour, A.; Mongin, F. *Synthesis* **2008**, 4033–4035. (c) Bentabed-Ababsa, G.; Blanco, F.; Derdour, A.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Ballesteros, R.; Abarca, B. *J. Org. Chem.* **2009**, *74*, 163–169. (d) Snégaroff, K.; L'Helgoual'ch, J.-M.; Bentabed-Ababsa, G.; Nguyen, T. T.; Chevallier, F.; Yonehara, M.; Uchiyama, M.; Derdour, A.; Mongin, F. *Chem.—Eur. J.* **2009**, *15*, 10280–10290.

(17) $CdCl_2$·TMEDA can be prepared in large amounts (~20 g) and stored for several months in a desiccator, whereas free $CdCl_2$ has to be heated with a heat gun under vacuum for 30 min before each use.

(18) (a) Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681–2682. (b) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155–6157.

(19) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276–9287.

(20) Using Me_3SiCl and I_2 as electrophile, difunctionalized derivatives concomitantly formed, probably through an homotransmetalation type mechanism: Mallet, M.; Quéguiner, G. *Tetrahedron* **1985**, *16*, 3433–3440.

(21) (a) Cailly, T.; Fabis, F.; Lemaitre, S.; Bouillon, A.; Rault, S. *Tetrahedron Lett.* **2005**, *46*, 135–137. (b) Cailly, T.; Fabis, F.; Bouillon, A.; Lemaître, S.; Sopkova, J.; de Santos, O.; Rault, S. *Synlett* **2006**, 53–56. See also: (c) Cailly, T.; Fabis, F.; Rault, S. *Tetrahedron* **2006**, *62*, 5862–5867. An in situ deprotonation−trapping protocol has also been used for the synthesis of the corresponding boronic esters: (d) Hansen, H. M.; Lysén, M.; Begtrup, M.; Kristensen, J. L. *Tetrahedron* **2005**, *61*, 9955–9960. (e) Cailly, T.; Lemaître, S.; Fabis, F.; Rault, S. *Synthesis* **2007**, 3247–3251. Note that butyllithium in a mixture of THF and hexane has also been used, albeit in a low yield, to metalate 4-cyanopyridine at the 2 position: (f) Su, Y.-J.; Ko, C.-W. Chinese Pat. 1616471, **2005**.

The deprotonation of cyanopyridines (**1**−**3**) as well as cyanopyrazine (**4**) was attempted using $(TMP)_3CdLi$ in THF (Table 1), with this base being suitable to metalate benzonitrile.[16a] Conducting the reaction from 2-cyanopyridine (**1**) using 0.5 equiv of base at 0 °C for 2 h resulted, after quenching with iodine, in the formation of a mixture from which the main compound, 2-cyano-3-iodopyridine (**5a**), was isolated in 39% yield (entry 1). When the reaction was carried out at room temperature, the iodide **5a** formed in 30% yield, due to the more important formation of side products (entry 2). By using 1 equiv of base at room temperature, the di- and triiodide **5b**,**c** were obtained in 28 and 20% yield, respectively (entry 3). If the formation of a diiodinated compound can be rationalized as the result of a dimetalation, $(TMP)_3CdLi$ being able to dideprotonate substrates such as pyrazine,[16b] thiazole,[16a] *N*-Boc pyrrole,[16a] thiophenes,[16a] and [1,2,3]triazolo[1,5-*a*]pyridines,[16c] the triiodide **5c** could rather result from a metalation of **5b** during the trapping step with iodine, as already suggested in the case of 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine.[16c]

The reaction from 4-cyanopyridine (**2**) was then attempted using 0.5 equiv of base at 0 °C for 2 h; subsequent trapping with iodine afforded a mixture of 4-cyano-3-iodo- and 4-cyano-3,5-diodopyridine (**6a**,**b**) in 30 and 20% yield, respectively (entry 4). By performing the reaction at room temperature, the diiodide was not observed, but a 72:28 ratio of 4-cyano-3-iodopyridine (**6a**) and isomeric 4-cyano-2-iodopyridine (**6c**) was obtained instead, the latter being isolated in 44 and 10% yield, respectively (entry 5). Surprisingly, carrying out the reaction with 1 equiv of base resulted in the formation of the diiodide **6d** under the same conditions (entry 6).

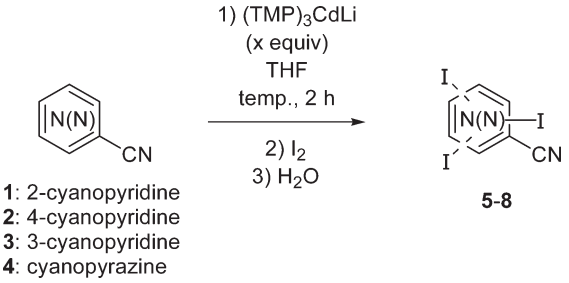
The results obtained with 3-cyanopyridine (**3**) were less disappointing. Indeed, when exposed to 0.5 equiv of base at room temperature for 2 h, this substrate was regioselectively metalated at the 2 position. This was demonstrated by subsequent interception with iodine to afford the derivative **7** in 61% yield (entry 7). This regioselectivity is different to that previously documented by other teams using LiTMP in THF at low temperatures; indeed, by using the lithium amide, the metalation took place unregioselectively at the positions adjacent to the cyano group.[19,21a] Such a result could be partly explained by the presence of a different directing group for the metalation using LiTMP than for that using $(TMP)_3CdLi$; whereas a first equivalent of LiTMP adds to the cyano group in the study performed by Rault et al., it does not seem to be the case with $(TMP)_3CdLi$ (Scheme 1).

These conditions were extended to cyanopyrazine (**4**) for which metalation mainly took place at the position next to the cyano group to furnish the iodide **8** in 43% yield (entry 8).

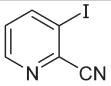
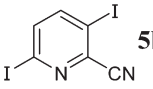
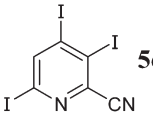
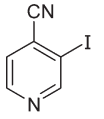
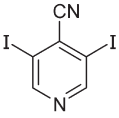
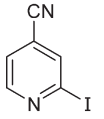
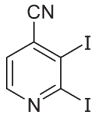
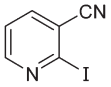
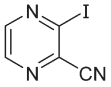
The compatibility of an ester function with $(TMP)_3CdLi$ in THF at room temperature has been recently evidenced with the possible metalation of methyl benzoate.[16a] Using ethyl thiophene-2-carboxylate (**9**) as substrate also resulted in its cadmation.[22] After a 2 h contact with 0.5 equiv of base followed by quenching with iodine, the 5-iodo derivative **10** was obtained in 77% yield (Scheme 2).

Deprotonation of ethyl pyridinecarboxylates is a much more difficult challenge due to easy nucleophilic attacks on their ring. In 2007, Knochel and co-workers reported the magnesiation of ethyl isonicotinate using $(TMP)_2Mg\cdot 2LiCl$ in THF at −40 °C for 12 h to give, after trapping with iodine, the corresponding 3-iodo derivative in 66% yield.[23]

TABLE 1. Deprotonation of 1−4 Using $(TMP)_3CdLi$ Followed by Trapping with I_2



1: 2-cyanopyridine
2: 4-cyanopyridine
3: 3-cyanopyridine
4: cyanopyrazine

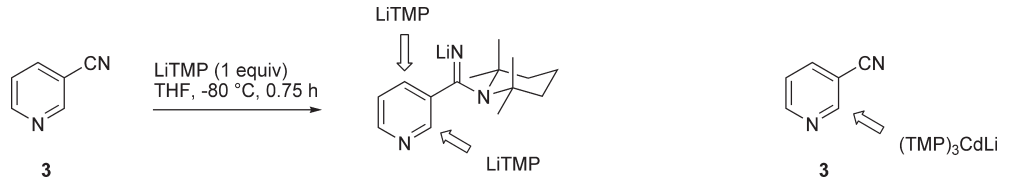
entry	substrate	x, temp.	product(s), yield(s)
1	**1**	0.5, 0 °C	 **5a**, 39%[a]
2	**1**	0.5, rt	**5a**, 30%[b]
3	**1**	1, rt	 **5b**, 28%
			 **5c**, 20%
4	**2**	0.5, 0 °C	 **6a**, 30%
			 **6b**, 20%
5	**2**	0.5, rt	**6a**, 44%
			 **6c**, 10%
6	**2**	1, rt	 **6d**, 51%
7	**3**	0.5, rt	 **7**, 61%
8	**4**	0.5, rt	 **8**, 43%[c]

[a]Other compounds including 2-cyano-3,4-diiodopyridine and 2-cyano-3,6-diiodopyridine were identified in the crude. [b]Other compounds including 2-cyano-6-iodopyridine and 2-cyano-3,6-diiodopyridine were identified in the crude. [c]A mixture of **8** and an unidentified diiodide was obtained in a 75:25 ratio.

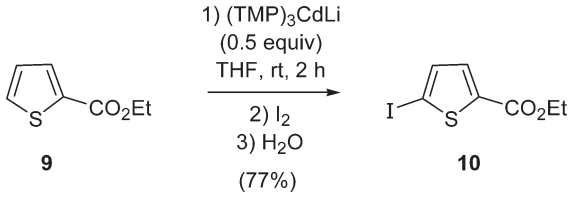
(22) Ethyl thiophene-2-carboxylate (**9**) has previously been metalated using $^{i}Pr_2NMgCl$ (2 equiv) in THF at room temperature for 10 min and trapped with iodine to provide the iodide **10** in 77% yield: Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 442–444.

(23) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681–7684.

SCHEME 1. 3-Cyanopyridine (3): Comparisons of the Species before Ring Deprotonation Using LiTMP and $(TMP)_3CdLi$



SCHEME 2. Functionalization of Ethyl Thiophene-2-carboxylate (9) Using $(TMP)_3CdLi$

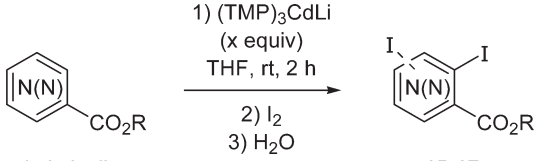


The deprotonation of the different pyridine or pyridazine esters **11**−**14** was attempted using $(TMP)_3CdLi$ in THF at room temperature for 2 h, and the metalated species was intercepted with iodine (Table 2). Conducting the reaction from ethyl picolinate (**11**) using 0.5 equiv of base resulted in the major formation of the 3-iodo derivative **15**, which was isolated in 58% yield (entry 1). Ethyl isonicotinate (**12**) similarly furnished the 3-iodo compound **16**, and the yield of 65% could be slightly improved to 72% using 1 equiv of base (entries 2 and 3). Surprisingly, methyl pyridazine-4-carboxylate (**13**) behaved differently when submitted to 0.5 equiv of base, with a complex mixture of mono- and diiodides formed (entry 4). When treated under the same conditions, ethyl nicotinate (**14**) allowed the synthesis of the 4-iodo derivative **17** (entry 5). The latter could not be isolated due its instability over silica gel but could be identified by NMR. It was involved without purification in a known copper-catalyzed reaction[24] with pyrazole to provide the expected derivative **18** in a two-step 38% yield (Scheme 3).

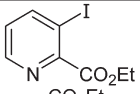
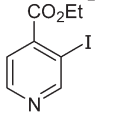
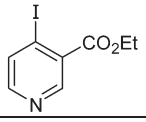
It was then decided to involve in the deprotonation−trapping sequence methyl pyridine-2,6-dicarboxylate (**19**). By using 0.5 equiv of $(TMP)_3CdLi$, the 3-iodo, 4-iodo and 3,4-diiodo derivatives **20**−**22** were obtained in a 63:28:9 ratio. Whereas the main compounds **20** and **21** were isolated from the mixture in 35 and 3% yield, respectively, methyl 3,4-diiodopyridine-2,6-dicarboxylate (**22**) was only identified from the NMR spectra of the crude. Turning to 1 equiv of base resulted in the formation of a fourth derivative, methyl 3,5-diiodopyridine-2,6-carboxylate (**23**), together with the previous iodides. It was isolated from the 22:25:4:49 mixture of the 3-iodo, 4-iodo, 3,5-diiodo, and 3,4-diiodo compounds in a modest 14% yield (Scheme 4).

Aiming to valorize the newly synthesized ethyl iodopyridinecarboxylates **15**−**17**, we studied their reactivity in palladium-catalyzed cross-coupling reactions. Especially, as done previously on ethyl halogenothiophenecarboxylates,[25] we decided to couple those compounds, as well as methyl 2-chloronicotinate (**24**), with 2-aminopyridines **25**−**27** in order to access to polycyclic compounds containing a pyridopyrimidinone moiety (Scheme 5 and Table 3).

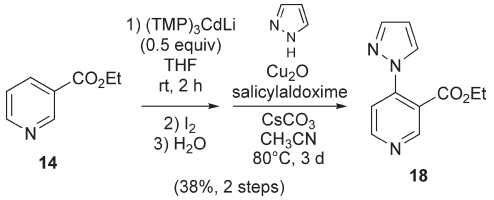
TABLE 2. Deprotonation of 11−14 Using $(TMP)_3CdLi$ Followed by Trapping with I_2



11: ethyl picolinate
12: ethyl isonicotinate
13: methyl pyridazine-4-carboxylate
14: ethyl nicotinate

entry	substrate	x	product, yield
1	**11**	0.5	 **15**, 58%
2	**12**	0.5	 **16**, 65%
3	**12**	1	**16**, 72%
4	**13**	0.5	mixture -
5	**14**	0.5	 **17**, -

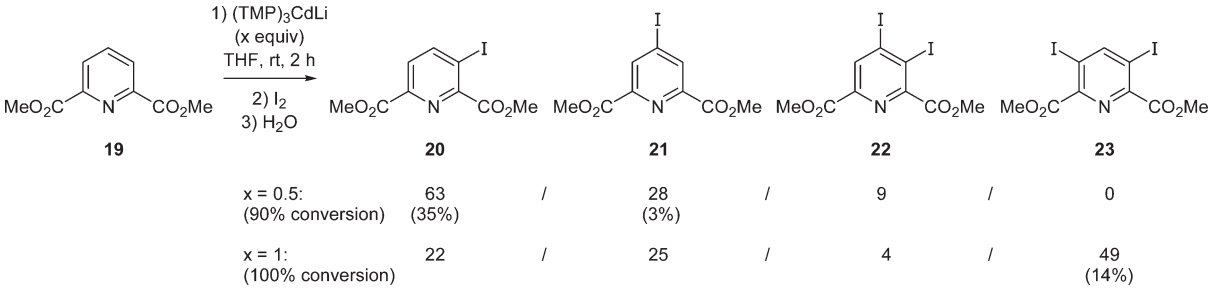
SCHEME 3. Synthesis of Ethyl 4-(pyrazol-1-yl)nicotinate (18)



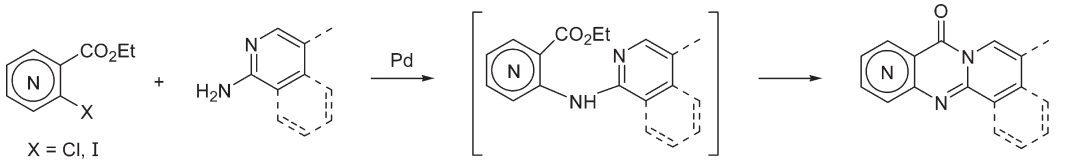
Indeed, the pyridopyrimidinone core is present in a number of biologically active substances. For example, aza analogues of methaqualone[26] and 2-substituted 3-arylpyrido[2,3-*d*]pyrimidinones[27] proved to be anticonvulsant agents, whereas some aza-quinazolinones[28] were described

(24) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695–709.
(25) Begouin, A.; Hesse, S.; Queiroz, M. J. R. P.; Kirsch, G. *Synthesis* **2006**, 2794–2798.
(26) Vaidya, N. A.; Panos, C. H.; Kite, A.; Ben Iturrian, W.; De Witt Blanton, C. *J. Med. Chem.* **1983**, *26*, 1422–1425.
(27) White, D. C.; Greenwood, T. D.; Downey, A. L.; Bloomquist, J. R.; Wolfe, J. F. *Bioorg. Med. Chem. Lett.* **2004**, 5711–5717.
(28) Johnson, M.; Li, A.-R.; Liu, J.; Fu, Z.; Zhu, L.; Miao, S.; Wang, X.; Xu, Q.; Huang, A.; Marcus, A.; Xu, F.; Ebsworth, K.; Sablan, E.; Danao, J.; Kumer, J.; Dairaghi, D.; Lawrence, C.; Sullivan, T.; Tonn, G.; Schall, T.; Collins, T.; Medina, J. *Bioorg. Med. Chem. Lett.* **2007**, 3339–3343.

SCHEME 4. Deprotonation of 19 Using $(TMP)_3CdLi$ Followed by Trapping with I_2



SCHEME 5. Synthetic Scheme for the Synthesis of Tricyclic (or Tetracyclic) Compounds

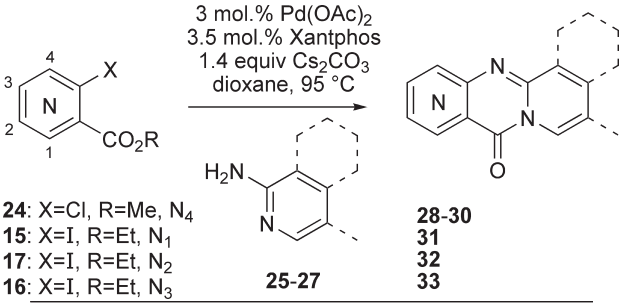


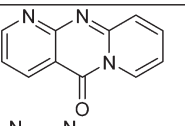
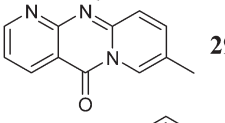
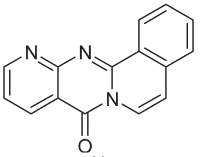
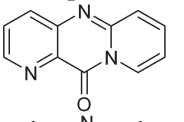
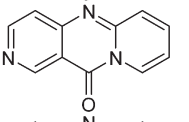
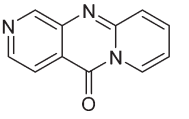
as antagonists of CXCR3. Aza-tryptanthrins exhibited antitrypanosomal activity[29] and inhibited *Plasmodium falciparum* cyclin-dependent kinases.[30]

Optimization of the reaction conditions was conducted by coupling methyl 2-chloronicotinate (**24**) with 2-aminopyridine (**25**). Whereas ethyl bromothiophenecarboxylates were very sensitive to the reaction conditions (several cycles of evacuation−backfilling with argon were needed) and required high catalyst loading (7 mol % of palladium acetate and 5 mol % of Xantphos), halogenopyridinecarboxylates gave good results using only 3 mol % of palladium acetate and 3.5 mol % of Xantphos. Moreover, a simple purge of argon was sufficient. The C−N coupling followed by the intramolecular cyclization involving the nitrogen atom of the pyridine ring and the carbonyl moiety of the carboxylate took place at room temperature but in a very low yield. Turning to 55 °C and 18 h of reaction allowed the formation of the expected product **28** in 20% yield. Finally, the best yield (66%) was obtained conducting the reaction at 95 °C for 24 h (entry 1). Those conditions were then extended to the use of 2-amino-5-methylpyridine (**26**) and 1-aminoisoquinoline (**27**). The methylated compound **29** was obtained after only 2.5 h of reaction in 79% yield (entry 2), and the tetracyclic compound **30** in a lower 43% yield (entry 3). Involving the iodo esters **15**−**17** in the reaction similarly resulted in the formation of the tricyclic compounds **31**−**33** (entries 4−6). Whereas **30**−**33** are new compounds, **28** and **29** were soon described in the literature;[31] they were obtained thanks to a two-step process including Ullman reaction of 2-halogenonicotinic acid with 2-aminopyridine-1-oxides and subsequent intramolecular cyclization of the resulting 3-carboxy-2,2′-bipyridylamin-1′-oxides using PCl_3.

Pharmacology. Applying the agar plate diffusion technique,[32] the newly synthesized compounds **28**−**33** were screened in vitro for their bactericidal activity against Gram positive bacteria (*Staphylococcus aureus*) and Gram negative

TABLE 3. Buchwald−Hartwig Cross-Coupling of 24, 15−17



entry	substrates	product, yield
1	**24** + **25**	 **28**, 66%
2	**24** + **26**	 **29**, 79%
3	**24** + **27**	 **30**, 43%
4	**15** + **25**	 **31**, 62%
5	**17** + **25**	 **32**, 50%[a]
6	**16** + **25**	 **33**, 52%

[a]For two steps.

(29) (a) Scovill, J.; Blank, E.; Konnick, M.; Nenortas, E.; Shapiro, T. *Antimicrob. Agents Chemother.* **2002**, *46*, 882–883. (b) Bhattacharjee, A. K.; Skancky, D. J.; Jennings, B.; Hudson, T. H.; Brendle, J. J.; Werbovetz, K. A. *Bioorg. Med. Chem.* **2002**, *10*, 1979–1989.

(30) Bhattacharjee, A. K.; Geyer, J. A.; Woodard, C. L.; Kathcart, A. K.; Nichols, D. A.; Prigge, S. T.; Mott, B. T.; Waters, N. C. *J. Med. Chem.* **2004**, *47*, 5418–5426.

(31) Rylowski, A.; Pucko, W. *Acta Pol. Pharm.* **1997**, *54*, 325–330.

(32) Bauer, A. W.; Mkriby, W. W.; Sherris, J. C.; Turck, M. *Am. J. Clin. Pathol.* **1966**, *45*, 493.

TABLE 4. Bactericidal and Fungicidal Activity of Compounds 28−33 and Ciprofloxacin and Nystin[a]

entry	compound	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeroginosa*	*Fusarium*	*Aspergillus niger*	*Candida albicans*
1	**28**	19 (++)	-	24 (++)	27 (+++)	-	22 (++)
2	**29**	18 (++)	-	19 (++)	17 (++)	-	16 (++)
3	**30**	-	-	-	56 (++++++)	18 (++)	19 (++)
4	**31**	16 (++)	-	-	-	-	18 (++)
5	**32**	17 (++)	18 (++)	25 (+++)	20 (++)	-	25 (+++)
6	**33**	17 (++)	-	25 (+++)	-	-	22 (++)
7	ciprofloxacin	+++	+++	+++			
8	nystin				+++	+++	+++

[a]The diameters of zones of inhibition are given in millimeters. Stock solution: 5 μg in 1 mL of DMF; 1 mL of stock solution in each hole of each paper disk. +: < 15 mm; ++: 15−24 mm; +++: 25−34 mm; ++++: 35−44 mm, etc.

TABLE 5. In Vitro Cytotoxic Activity (IC_{50}) of Compounds 18, 28−33, and Doxorubicin Against a Liver Carcinoma Cell Line (HEPG2), a Human Breast Carcinoma Cell Line (MCF7), and a Cervix Carcinoma Cell Line (HeLa)[a]

entry	compound	HEPG2 ($\mu g \cdot mL^{-1}$)	MCF7 ($\mu g \cdot mL^{-1}$)	HeLa ($\mu g \cdot mL^{-1}$)
1	**18**	0.89	2.38	1.51
2	**28**	1.70	0.78	1.39
3	**29**	2.27	2.99	3.11
4	**30**	1.77	1.73	1.09
5	**31**	1.47	2.50	3.26
6	**32**	1.81	2.34	2.31
7	**33**	1.58	1.96	1.70
8	doxorubicin	0.60	0.70	0.85

[a]IC_{50} is defined as the concentration which results in a 50% decrease in cell number as compared with that of the control structures in the absence of an inhibitor.

bacteria (*Escherichia coli* and *Pseudomonas aeroginosa*) and for their fungicidal activity against *Fusarium*, *Aspergillus niger*, and *Candida albicans* (Table 4). The compounds **32** and **33** showed a good bactericidal activity, similar to that of ciprofloxacin, against *Pseudomonas aeroginosa*, whereas **28** and **30** showed a good fungicidal activity, similar to that of nystin, against *Fusarium* and **32** against *Candida albicans*.

The compounds **18** and **28−33** were also tested against a human liver carcinoma cell line (HEPG2), a human breast carcinoma cell line (MCF7), and a cervix carcinoma cell line (HeLa) (Table 5). Moderate cytotoxic activities were observed; the compounds **18** and **28** were found to have more promising activities toward HEPG2 and MCF7, respectively, compared to a reference drug (doxorubicin).

Conclusion

All pyridine nitriles and esters were metalated at the position next to the directing group using 0.5 equiv of $(TMP)_3CdLi$ in tetrahydrofuran at room temperature for 2 h. Subsequent trapping with iodine afforded the iodo derivatives in yields ranging from 30 to 65%. The ethyl iodopyridinecarboxylates thus obtained were then involved in a one-pot palladium-catalyzed cross-coupling reaction/cyclization using 2-aminopyridine to afford new polycyclic compounds containing a pyridopyrimidinone moiety, which were evaluated for their bactericidal and fungicidal activity. Some of the newly synthesized compounds were tested for their antitumor activity.

Because of the toxicity of cadmium compounds,[33] the use of other ate bases was before considered. Polar mixtures including alkali (or alkaline-earth metal) were ruled out because of their lack of compatibility with both reactive functions and sensitive aromatic heterocycles. Lithium aluminate and cuprate were similarly discarded, sensitive heterocycles being converted with these bases at low temperatures.[12,15] The 1:1 LiTMP/$(TMP)_2Zn$ lithium−zinc combination, prepared from $ZnCl_2 \cdot TMEDA$ and 3 equiv of LiTMP, allows efficient deprotonation reactions of aromatic substrates.[34] Nevertheless, it was not employed here because reactions using it are, in general, more weakly chemoselective,[16b] probably due to the presence of free LiTMP. Real lithium zincates could be more suitable for the functionalization of heteroaromatic esters and nitriles; studies in order to identify bases allowing more efficient and chemoselective reactions are currently under investigation.

Experimental Section

General Procedure A (Deprotonation Using 0.5 equiv of $CdCl_2 \cdot TMEDA$ and 1.5 equiv of LiTMP Followed by Trapping Using I_2). To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.52 mL, 3.0 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 3.0 mmol) and, 5 min later, $CdCl_2 \cdot TMEDA$[35] (0.30 g, 1.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at room temperature, a solution of I_2 (0.76 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

General Procedure B (Deprotonation Using 1.0 equiv of $CdCl_2 \cdot TMEDA$ and 3.0 equiv of LiTMP Followed by Trapping Using I_2). To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.1 mL, 6.0 mmol) in THF (5 mL) were successively added BuLi (1.6 M hexanes solution, 6.0 mmol) and, 5 min later, $CdCl_2 \cdot TMEDA$[35] (0.60 g, 2.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at room temperature, a solution of I_2 (1.5 g, 6.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

(33) Shannon, M. Heavy Metal Poisoning. In *Clinical Management of Poisoning and Drug Overdose*, 3rd ed.; Haddad, L. M., Shannon, M., Winchester, J. F., Eds.; W.B. Saunders: Philadelphia, PA, 1998. The use of salts reduces the risk of cadmium absorption.

(34) L'Helgoual'ch, J.-M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177−183 and references cited therein.

(35) $CdCl_2 \cdot TMEDA$ was prepared as described: Kedarnath, G.; Kumbhare, L. B.; Jain, V. K.; Phadnis, P. P.; Nethaji, M. *Dalton Trans.* **2006**, 2714–2718.

2-Cyano-3-iodopyridine (5a).[21a] **5a** was obtained according to the general procedure A starting from 2-cyanopyridine (0.21 g), but keeping the metalation temperature at 0 °C, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 80/20) as a white powder (0.18 g, 39%): mp 98 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26 (dd, 1 H, J = 8.2 and 4.6 Hz), 8.24 (dd, 1 H, J = 8.2 and 1.4 Hz), 8.68 (dd, 1 H, J = 4.6 and 1.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 117.4, 127.5, 137.9, 138.5, 146.6, 149.4; HRMS calcd for $C_6H_3IN_2$ ($M^{+\bullet}$) 229.9341, found 229.9345.

2-Cyano-6-iodopyridine was identified by its ^{1}H NMR spectra (300 MHz, $CDCl_3$): δ 7.49 (t, 1 H, J = 7.8 Hz), 7.68 (dd, 1 H, J = 7.6 and 1.0 Hz), 7.95 (dd, 1 H, J = 7.8 and 1.0 Hz).

2-Cyano-3,4-diiodopyridine was identified by its ^{1}H NMR spectra (300 MHz, $CDCl_3$): δ 7.62 (d, 1 H, J = 8.4 Hz), 7.79 (d, 1 H, J = 8.4 Hz).

2-Cyano-3,6-diiodopyridine (5b).[21a] **5b** was obtained according to the general procedure B starting from 2-cyanopyridine (0.21 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 90/10) as a beige powder (0.20 g, 28%): mp 140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 1 H, J = 8.4 Hz), 7.80 (d, 1 H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.7, 116.3, 116.5, 139.1, 140.0, 147.5; HRMS calcd for $C_6H_3I_2N_2$ ($[M + H]^+$) 356.8386, found 356.8387.

2-Cyano-3,4,6-triiodopyridine (5c). 5c was obtained according to the general procedure B starting from 2-cyanopyridine (0.21 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 90/10) as a yellow powder (0.19 g, 20%): mp 211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.2, 115.9, 117.0, 122.4, 139.7, 147.1; HRMS calcd for $C_6H_2I_3N_2$ ($[M + H]^+$) 482.7352, found 482.7352.

4-Cyano-3-iodopyridine (6a).[21a] **6a** was obtained according to the general procedure A starting from 4-cyanopyridine (0.21 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 70/30) as a beige powder (0.20 g, 44%): mp 122 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (dd, 1 H, J = 4.8 and 0.6 Hz), 8.71 (d, 1 H, J = 5.0 Hz), 9.10 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.4, 117.0, 127.1, 127.9, 148.9, 158.0; HRMS calcd for $C_6H_3IN_2$ ($M^{+\bullet}$) 229.9341, found 229.9345.

4-Cyano-3,5-diiodopyridine (6b).[21a] **6b** was obtained according to the general procedure A starting from 4-cyanopyridine (0.21 g), but keeping the metalation temperature at 0 °C, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 90/10) as a beige powder (0.14 g, 20%): mp 153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.3 (2C), 118.4, 134.5, 156.4 (2C); HRMS calcd for $C_6H_2I_2N_2Na$ ($[M + Na]^+$) 378.8205, found 378.8207.

4-Cyano-2-iodopyridine (6c).[36] **6c** was obtained according to the general procedure A starting from 4-cyanopyridine (0.21 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 70/30) as a beige powder (46 mg, 10%): mp 76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1 H, J = 5.0 and 1.4 Hz), 7.96 (t, 1 H, J = 1.4 Hz), 8.56 (dd, 1 H, J = 5.0 and 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.6, 117.8, 121.5, 124.1, 136.0, 151.3; HRMS calcd for $C_6H_3IN_2$ ($M^{+\bullet}$) 229.9341, found 229.9345.

4-Cyano-2,3-diiodopyridine (6d). 6d was obtained according to the general procedure B starting from 4-cyanopyridine (0.21 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 80/20) as a beige powder (0.36 g, 51%): mp 215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1 H, J = 5.3 Hz), 8.08 (d, 1 H, J = 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.6, 119.1, 121.0, 127.1, 133.1, 151.7; HRMS calcd for $C_6H_2I_2N_2$ ($M^{+\bullet}$) 355.8307, found 355.8341.

3-Cyano-2-iodopyridine (7). 7 was obtained according to the general procedure A starting from 3-cyanopyridine (0.21 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 80/20) as a beige powder (0.28 g, 61%): mp 127 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43 (dd, 1 H, J = 7.7 and 4.9 Hz), 7.82 (dd, 1 H, J = 7.7 and 2.0 Hz), 8.54 (dd, 1 H, J = 4.9 and 2.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 117.7, 119.9, 121.0, 122.5, 141.2, 152.9; HRMS calcd for $C_6H_3IN_2$ ($M^{+\bullet}$) 229.9341, found 229.9345. These data are analogous to those previously described.[19]

2-Cyano-3-iodopyrazine (8).[37] **8** was obtained according to the general procedure A starting from cyanopyrazine (0.21 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 90/10) as a yellow powder (0.20 g, 43%): mp 107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, 1 H, J = 2.4 Hz), 8.65 (d, 1 H, J = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.3, 120.7, 138.2, 143.2, 147.2; HRMS calcd for $C_5H_2IN_3Na$ ($[M + Na]^+$) 253.9191, found 253.9192.

Ethyl 5-iodothiophene-2-carboxylate (10). 10 was obtained according to the general procedure A starting from ethyl thiophene-2-carboxylate (0.31 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 90/10) as a yellow oil (0.43 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3 H, J = 7.1 Hz), 4.33 (q, 2 H, J = 7.1 Hz), 7.25 (d, 1 H, J = 3.9 Hz), 7.42 (d, 1 H, J = 3.9 Hz); these data are similar to those described;[22] ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 61.5, 82.6, 134.4, 137.8, 139.8, 161.0.

Ethyl 3-iodopicolinate (15).[38] **15** was obtained according to the general procedure A starting from ethyl picolinate (0.30 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 80/20) as a yellow oil (0.32 g, 58%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (t, 3 H, J = 7.1 Hz), 4.47 (q, 2 H, J = 7.1 Hz), 7.11 (dd, 1 H, J = 8.2 and 4.7 Hz), 8.25 (dd, 1 H, J = 8.2 and 1.4 Hz), 8.62 (dd, 1 H, J = 4.7 and 1.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 62.1, 92.1, 126.1, 126.2, 148.2, 152.3, 165.7; HRMS calcd for $C_8H_8INO_2$ ($M^{+\bullet}$) 276.9600, found 276.9609.

Ethyl 3-iodoisonicotinate (16).[23] **16** was obtained according to the general procedure A starting from ethyl isonicotinate (0.30 g) and isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 80/20) as an orange oil (0.36 g, 65%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (t, 3 H, J = 7.1 Hz), 4.42 (q, 2 H, J = 7.1 Hz), 7.62 (d, 1 H, J = 4.9 Hz), 8.60 (d, 1 H, J = 4.8 Hz), 9.08 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 62.4, 92.3, 124.3, 142.3, 149.0, 159.4, 164.9; HRMS calcd for $C_8H_8INO_2$ ($M^{+\bullet}$) 276.9600, found 276.9609.

Methyl 3-iodopyridazine-4-carboxylate. A pure fraction was isolated (eluent: heptane/EtOAc 85/15) from the crude obtained according to the general procedure A as a yellow solid (degradation to a dark residue upon standing): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1 H, J = 5.0 Hz), 9.26 (d, 1 H, J = 5.0 Hz), 4.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.7, 77.4, 126.2, 135.3, 150.6, 164.4.

Methyl 3,5-diiodopyridazine-4-carboxylate. A pure fraction was isolated (eluent: heptane/EtOAc 85/15) from the crude obtained according to the general procedure A as a yellow solid (degradation to a dark residue upon standing): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1 H), 4.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.1, 97.4, 120.2, 145.6, 157.9, 165.4.

(36) Jones, P.; Kinzel, O.; Llauger Bufi, L.; Muraglia, E.; Pescatore, G.; Torrisi, C. PCT Int. Appl. WO2007138355, **2007**.

(37) Rodgers, J. D.; Robinson, D. J.; Arvanitis, A. G.; Maduskuie, T. P., Jr.; Shepard, S.; Storace, L.; Wang, H.; Rafalski, M.; Jalluri, R. K.; Combs, A. P. PCT Int. Appl. WO2005105814, **2005**.

(38) Giblin, G. M. P.; Hall, A.; Hurst, D. N. PCT Int. Appl. WO2005037794, **2005**.

Ethyl 4-iodonicotinate (17). 17 was obtained according to the general procedure A starting from ethyl nicotinate (0.30 g) but could not be purified by flash chromatography on silica gel because of its low stability. It was identified by NMR: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, 3 H, J = 7.1 Hz), 4.14 (q, 2 H, J = 7.1 Hz), 7.94 (d, 1 H, J = 5.3 Hz), 8.23 (d, 1 H, J = 5.3 Hz), 8.93 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 62.1, 106.1, 131.0, 136.2, 151.0, 152.0, 164.7. The crude was directly involved in the reactions giving the compounds **18** and **32**.

Ethyl 4-(pyrazol-1-yl)nicotinate (18). 18 was obtained from the crude compound **17** by adapting a procedure described[24] and was isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 70/30) as an orange oil (0.17 g, two steps, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3 H, J = 7.1 Hz), 4.31 (q, 2 H, J = 7.2 Hz), 6.50 (dd, 1 H, J = 2.4 and 1.8 Hz), 7.48 (d, 1 H, J = 5.4 Hz), 7.75 (d, 1 H, J = 1.5 Hz), 7.83 (d, 1 H, J = 2.7 Hz), 8.75 (d, 1 H, J = 5.1 Hz), 8.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 62.1, 108.8, 117.1, 121.9, 129.5, 142.6, 145.1, 151.5, 152.9, 165.9; HRMS calcd for $C_{11}H_{12}N_3O_2$ ([M + H]$^+$) 218.0930, found 218.0932.

Methyl 3-iodopyridine-2,6-dicarboxylate (20). 20 was obtained according to the general procedure A starting from methyl pyridine-2,6-dicarboxylate (0.39 g) and isolated by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 80/20) as a pale orange powder (0.22 g, 35%): mp 88−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 3 H), 4.01 (s, 3 H), 7.89 (d, 1 H, J = 8.1 Hz), 8.42 (d, 1 H, J = 8.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.3 (2C), 95.3, 127.1, 146.8, 149.6, 152.6, 164.7, 165.5; HRMS calcd for $C_9H_8INO_4$ ($M^{+\bullet}$) 320.9498, found 320.9496.

Methyl 4-iodopyridine-2,6-dicarboxylate (21). 21 was obtained according to the general procedure A starting from methyl pyridine-2,6-dicarboxylate (0.39 g) and isolated by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 80/20) in 3% (18 mg) yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 6H), 8.66 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.2 (2C), 106.8, 136.9 (2C), 148.0 (2C), 163.6 (2C); these data are similar to those previously described;[39] HRMS calcd for $C_7H_6INO_2$ [(M − $C_2H_2O_2$)$^{+\bullet}$] 262.9443, found 262.9469.

Methyl 3,4-diiodopyridine-2,6-dicarboxylate (22). 22 formed using the general procedures A and B and was identified by its NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 6H), 8.88 (s, 1H); HRMS calcd for $C_8H_5I_2NO_3$ [(M − CH_2O)$^{+\bullet}$] and $C_7H_5I_2NO_2$ [(M − $C_2H_2O_2$)$^{+\bullet}$] 416.8359 and 388.8410, found 416.8379 and 388.8426.

Methyl 3,5-diiodopyridine-2,6-dicarboxylate (23). 23 was obtained according to the general procedure B starting from methyl pyridine-2,6-dicarboxylate (0.39 g) and isolated by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 80/20) as a beige powder (0.13 g, 14%): mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (s, 6 H), 8.88 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.4 (2C), 93.4 (2C), 150.6, 159.5, 164.9 (2C); HRMS calcd for $C_9H_7I_2NO_4$ ($M^{+\bullet}$) 446.8465, found 446.8447.

General Procedure C for Buchwald−Hartwig Cross-Coupling. A solution of $Pd(OAc)_2$ (10 mg, 3 mol %), Xantphos (30 mg, 3.5 mol %), and Cs_2CO_3 (675 mg, 1.4 equiv) was prepared under argon in dioxane. When the temperature reached 55 °C, the appropriate halogenopyridine (1.5 mmol, 1 equiv) was added under argon, and then 5−10 min later (temperature about 80 °C), the aminopyridine (1.8 mmol, 1.2 equiv) was finally introduced. The reaction mixture was stirred at 95 °C for 2.5 to 24 h under argon (reaction was followed by thin layer chromatography). After cooling to room temperature, the reaction mixture was filtered, and the cake was washed with EtOAc. The filtrate was concentrated under reduced pressure.

Dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (28). 28 was obtained according to the general procedure C starting from methyl 2-chloronicotinate (0.26 g) and 2-aminopyridine (0.17 g) and was isolated after purification by chromatography on silica gel ($CHCl_3$ as eluent) as a yellow solid (0.20 g, 66%): mp 220−221 °C (lit.[40] 223 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99 (m, 1 H), 7.43 (dd, 1 H, J = 8.0 and 4.4 Hz), 7.64−7.69 (m, 2H), 8.78 (dd, 1 H, J = 8.0 and 2.1 Hz), 8.89 (m, 1 H), 9.12 (dd, 1 H, J = 4.4 and 2.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 111.3, 113.5, 120.6, 126.7, 127.0, 135.7, 137.0, 149.8, 157.4, 157.8, 159.7; IR (KBr) ν 1698, 1641, 1593, 1543, 1526, 1411 cm^{-1}; HRMS calcd for $C_{11}H_8N_3O$ ([M + H]$^+$) 198.0662, found 198.0668.

8-Methyldipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (29). 29 was obtained according to the general procedure C starting from methyl 2-chloronicotinate (0.26 g) and 2-amino-5-methylpyridine (0.19 g) and was isolated after purification by chromatography on silica gel ($CHCl_3$ as eluent) as a yellow solid (0.25 g, 79%): mp 201−202 °C (lit.[40] 203 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 6.82 (dd, 1 H, J = 7.5 and 1.8 Hz), 7.38 (dd, 1 H, J = 8.0 and 4.4 Hz), 7.45 (br s, 1 H), 8.74 (dd, 1 H, J = 8.0 and 2.1 Hz), 8.79 (d, 1 H, J = 7.5 Hz), 9.08 (dd, 1 H, J = 4.4 and 2.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.6, 110.9, 116.5, 120.1, 124.4, 126.0, 137.0, 147.8, 149.9, 157.7, 157.8, 159.8; IR (KBr) ν 1693, 1651, 1592, 1543, 1412 cm^{-1}; HRMS calcd for $C_{12}H_{10}N_3O$ ([M + H]$^+$) 212.0818, found 212.0826.

Pyrido[2′,3′:4,5]pyrimidino[2,1-*a*]isoquinolin-8-one (30). 30 was obtained according to the general procedure C starting from methyl 2-chloronicotinate (0.26 g) and 1-aminoisoquinoline (0.26 g) and was isolated after purification by chromatography on silica gel (eluent: EtOAc/C_6H_{12} 70/30) as a yellow solid (95 mg, 43%): mp 242−244 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.17 (d, 1 H, J = 7.8 Hz), 7.48 (dd, 1 H, J = 8.0 and 4.5 Hz), 7.70−7.83 (m, 3 H), 8.67 (d, 1 H, J = 7.8 Hz), 8.81 (dd, 1 H, J = 8.0 and 2.1 Hz), 9.13 (dd, 1 H, J = 4.5 and 2.1 Hz), 9.30 (d, 1 H, J = 8.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 112.8, 114.2, 121.2, 121.5, 126.5, 127.0, 128.2, 128.9, 133.1, 133.4, 137.0, 149.1, 156.9, 157.2, 160.1; IR (KBr) ν 1679, 1645, 1593, 1555, 1423 cm^{-1}; HRMS calcd for $C_{15}H_{10}N_3O$ ([M + H]$^+$) 248.0818, found 248.0808.

Dipyrido[1,2-*a*:3′,2′-*d*]pyrimidin-11-one (31). 31 was obtained according to the general procedure C starting from ethyl 3-iodopicolinate (0.42 g) and 2-aminopyridine (0.17 g) and was isolated after purification by chromatography on silica gel ($CHCl_3$ as eluent) as a yellow solid (0.12 g, 62%): mp 211 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.94−7.00 (m, 1 H), 7.55−7.67 (m, 2 H), 7.75 (dd, 1 H, J = 8.5 and 4.1 Hz), 8.14 (dd, 1 H, J = 8.5 and 1.5 Hz), 8.91 (dd, 1 H, J = 4.1 and 1.5 Hz), 9.00−9.04 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 113.1, 126.3, 127.4, 129.0, 132.5, 135.1, 135.3, 145.6, 148.2, 148.9, 157.7; IR (KBr) ν 1702, 1641, 1543, 1519, 1469, 1413 cm^{-1}; HRMS calcd for $C_{11}H_8N_3O$ ([M + H]$^+$) 198.0662, found 198.0662.

Dipyrido[1,2-*a*:4′,3′-*d*]pyrimidin-11-one (32). 32 was obtained according to the general procedure C starting from crude ethyl 4-iodonicotinate (general procedure A) and 2-aminopyridine (0.23 g) and was isolated after purification by chromatography on silica gel (eluent: CH_2Cl_2/Et_3N 98/2) as a brown solid (0.20 g, 50% for two steps): mp 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (m, 1H), 7.54 (m, 2H), 7.68 (ddd, 1H, J = 9.2, 6.5, and 1.6 Hz), 8.80 (d, 1H, J = 6.0 Hz), 8.93 (m, 1H), 9.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.9, 113.7, 119.7, 126.4, 127.2, 139.4, 151.1, 152.0, 152.7, 152.9, 158.2; HRMS calcd for $C_{11}H_7N_3O$ ([M + H]$^+$) 198.0667, found 198.0670.

Dipyrido[1,2-*a*:3′,4′-*d*]pyrimidin-5-one (33). 33 was obtained according to the general procedure C starting from ethyl 3-iodoisonicotinate (0.42 g) and 2-aminopyridine (0.17 g) and was isolated after purification by chromatography on silica gel (eluent: CH_2Cl_2/Et_3N 98/2) as an orange solid (0.15 g, 52%): mp 164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (m, 1H), 7.59

(39) Storm, O.; Lüning, U. *Eur. J. Org. Chem.* **2002**, 3680–3685.

(40) Rylowski, A.; Pucko, W. *Acta Pol. Pharm.* **1997**, *54*, 325–330.

(m, 2H), 8.14 (dd, 1H, J = 5.4 and 0.7 Hz), 8.62 (br d, 1H, J = 5.4 Hz), 8.86 (dt, 1H, J = 7.4 and 1.2 Hz), 9.25 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.8, 118.6, 120.2, 126.8, 127.0, 135.1, 143.1, 143.7, 149.1, 151.9, 158.3; HRMS calcd for $C_{11}H_7N_3O$ ($[M + H]^+$) 198.0667, found 198.0672.

Pharmacology. Applying the agar plate diffusion technique,[32] the compounds were screened in vitro for their bactericidal activity against Gram positive bacteria (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeroginosa*) and for their fungicidal activity against *Fusarium*, *Aspergillus niger*, and *Candida albicans*. In this method, a standard 5 mm diameter sterilized filter paper disk impregnated with the compound (0.3 mg/0.1 mL of DMF) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 h at 37 °C for bacteria and 28 °C for fungi. The zone of inhibition of bacterial and fungi growth around the disk was observed.

The compounds were tested against a liver carcinoma cell line (HEPG2), a human breast carcinoma cell line (MCF7), and a cervix carcinoma cell line (HeLa). The method applied is similar to that reported by Skehan et al.[41] using 20 sulfo-rhodamine-B stain (SRB). Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the test compound to allow attachment of cell to the wall of the plate. Different concentrations of the compound under test (0, 1.0, 2.5, 5.0, and 10 μg/mL) were added to the cell monolayer in triplicate wells in individual dose, and monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed, and stained with SRB stain, excess stain was washed with acetic acid, and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an ELISA reader, and the relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after the specified compound and the IC_{50} was calculated.

(41) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst*. **1990**, *82*, 1107–1112.

Acknowledgment. We are grateful to Région Bretagne (France) and to MESRS (Algeria) for financial support to G.B., and to MESR (France) for financial support to T.T.N. We thank Rennes Métropole. We are also grateful to Faculty of Women, Ain Shams University, and National Institute of Cancer, Cairo University (Egypt) for pharmacological measurements.

Supporting Information Available: General procedures and copies of the ^{1}H and ^{13}C NMR spectra for compounds **5a**−**c**, **6a**−**d**, **7**, **8**, **10**, **15**−**18**, **20**, **23**, **28**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.