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One-Pot Coupling–Cyclization–Alkylation Synthesis of 1,2,5-Trisubstituted 7-Azaindoles in a Consecutive Three-component Fashion

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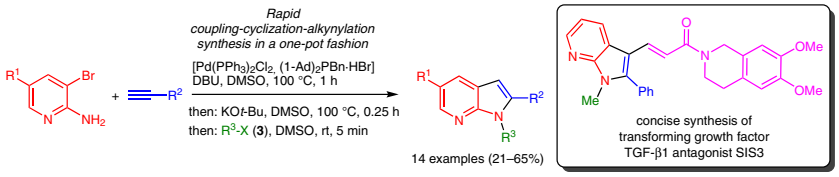

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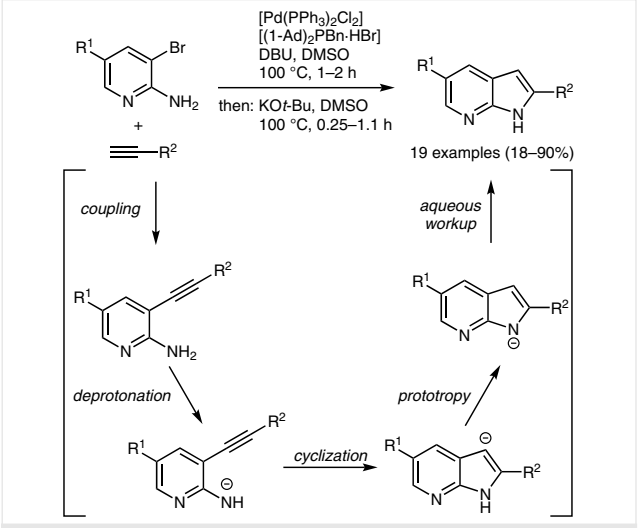
Abstract 1,2,5-Trisubstituted 7-azaindoles are rapidly and efficiently prepared in a one-pot, copper-free alkynylation–cyclization–alkylation sequence starting from unprotected 2-aminopyridyl halides in a consecutive three-component fashion. By extension to a consecutive four-component coupling–cyclization–iodination–alkylation synthesis of 3-iodo-1-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine, a concise synthesis of SIS3, a selective TGF-β1 and signaling inhibitor, was realized.

Key words 7-azaindoles, alkylation, alkynylation, cyclization, multicomponent reaction

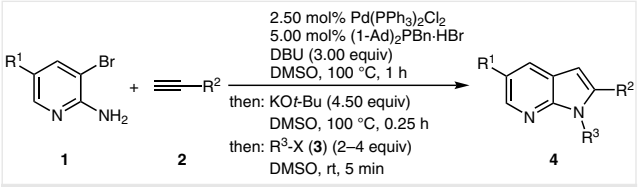
The steadily increasing insight into cancer metabolism has revealed that kinase inhibitors are promising targets[1] for identifying and developing privileged scaffolds[2] as novel anticancer agents.[3] Among many structures, 7-azaindoles, i.e., 1*H*-pyrrolo[2,3-*b*]pyridines, constitute a particularly interesting biheterocyclic scaffold[4] with enormous potency as kinase inhibitors.[5] As a consequence, a steady demand for synthetic strategies toward 7-azaindoles has become an ongoing evergreen.[6] For enhancing library design and thereby to lead-finding and development, the strategic concept of multicomponent reactions (MCR),[7] i.e., one-pot processes exploiting the perpetual generation of relative reactivity as a reactivity based principle in a domino, sequential or consecutive fashion,[8] has turned out to be particularly favorable. Surprisingly, MCR and one-pot syntheses of 7-azaindole derivatives have remained relatively unexplored to date.[9]

Recently, we reported a copper-free Pd-catalyzed alkynylation–cyclization synthesis of 2-substituted 7-azaindoles in a one-pot fashion starting from 2-amino-3-bromopyridines void of additional nitrogen protection or activation (Scheme 1).[10] Two compatible bases enable this efficient transformation, in which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is well suited for the alkynylation step. The employed second base KO*t*-Bu is by 6–8 pK_a units more basic than DBU,[11] both in water (19.0) and in DMSO (32.2).[12] Therefore, the 2-aminopyridine (pK_a in DMSO: 27.7)[12] will be quantitatively deprotonated to undergo a 5-*endo*-dig cyclization and subsequent prototropy to furnish the corresponding base of the 7-azaindole (with an estimated pK_a of 19 in DMSO). Since the reaction medium essentially contains this anion prior to workup, we reasoned that this strongly nucleophilic intermediate should be perfectly suited for concatenating a terminal electrophilic trapping, and thereby furnishing 1,2,5-trisubstituted 7-azaindoles in a consecutive three-component fashion.



Scheme 1 One-pot copper-free Pd-catalyzed alkynylation–cyclization synthesis of 2-substituted 7-azaindoles and tentative mechanistic rationale

Upon reaction of 2-amino-3-bromopyridines **1** and terminal alkynes **2** in DMSO at 100 °C for 1–2 h in the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ and cataCXium® A Bn·HBr as a ligand,[13] the alkynylation product was further reacted with KO*t*-Bu at 100 °C for 15 minutes and subsequently with a trapping electrophile **3** at room temperature for five minutes to furnish, after aqueous workup and purification, the 1,2,5-trisubstituted 7-azaindoles **4** in 21–65% isolated yield (Scheme 2, Table 1).[14] The structures of all previously unreported compounds were unambiguously assigned by spectroscopic methods (^{1}H NMR and ^{13}C NMR, IR) and by combustion analysis. The employed three points of diversity can be substituted alkyl and halide substituents (R^1), aliphatic and aromatic moieties (R^2), and arylmethyl and functionalized alkyl substituents (R^3), and the obtained isolated yields refer to a quite efficient sequence with an average yield of 59–87% per bond-forming step.



Scheme 2 Three-component coupling–cyclization–alkylation synthesis of 1,2,5-trisubstituted 7-azaindoles **4**

Table 1 One-Pot, Three-Component Synthesis of 1,2,5-Trisubstituted 7-Azaindoles **4**

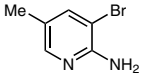
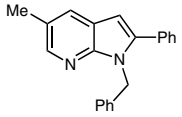
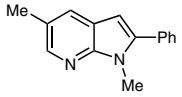
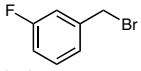
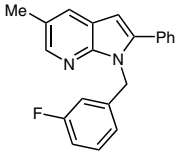
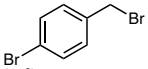
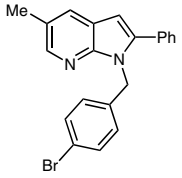
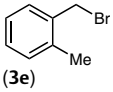
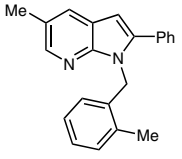
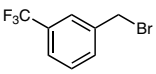
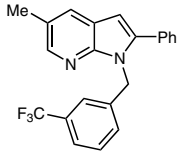
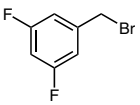
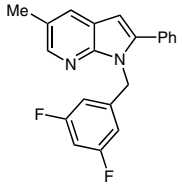
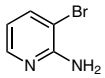
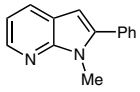
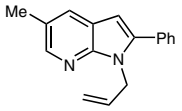
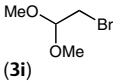
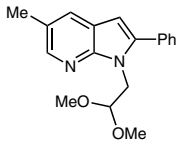
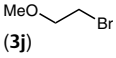
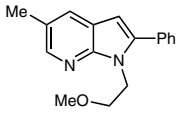
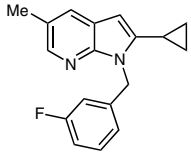
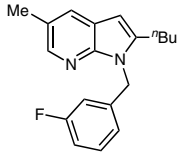
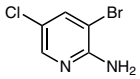
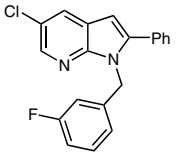
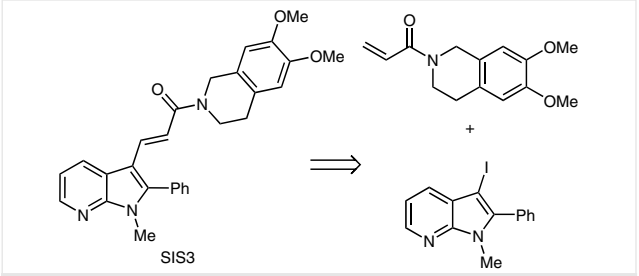
Entry	2-Amino-3-bromopyridine **1**	Alkyne **2**	Electrophile **3**	1,2,5-Trisubstituted 7-azaindole	Yield (%)[a]
1	 (**1a**)	 (**2a**)	$PhCH_2Br$ (**3a**)		**4a** (32)
2	**1a**	**2a**	MeI (**3b**)		**4b** (65)
3	**1a**	**2a**	 (**3c**)		**4c** (52)
4	**1a**	**2a**	 (**3d**)		**4d** (49)
5	**1a**	**2a**	 (**3e**)		**4e** (27)
6	**1a**	**2a**	 (**3f**)		**4f** (21)
7	**1a**	**2a**	 (**3g**)		**4g** (65)[b]

Table 1 (continued)

Entry	2-Amino-3-bromopyridine **1**	Alkyne **2**	Electrophile **3**	1,2,5-Trisubstituted 7-azaindole	Yield (%)[a]
8[a]	 (**1b**)	**2a**	**3b**		**4h** (57)
9	**1a**	**2a**	 (**3h**)		**4i** (34)
10[b]	**1a**	**2a**	 (**3i**)		**4j** (34)
11	**1a**	**2a**	 (**3j**)		**4k** (38)
12	**1a**	 (**2b**)	**3c**		**4l** (43)
13	**1a**	 (**2c**)	**3c**		**4m** (28)
14	 (**1c**)	**2a**	**3c**		**4n** (61)

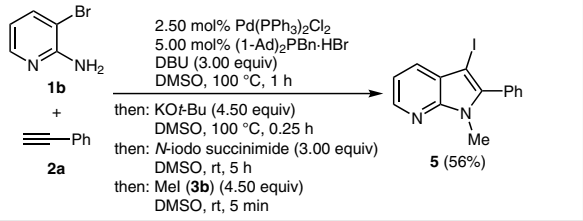
[a] After addition of the electrophile the mixture was stirred at rt for 2.5 h.
[b] After addition of electrophile **3i** the reaction mixture was stirred at 100 °C for 23 h.

The scalability of this novel one-pot three-component synthesis of 1,2,5-trisubstituted 7-azaindoles as illustrated for compound **4h** encouraged us to probe the concept using Lautens' final step in the synthesis of SIS3 (Scheme 3),[15] a potent and selective TGF-β1 and signaling inhibitor that suppresses Smad3 phosphorylation.[16] Lautens' appealing synthesis uses a terminal Heck reaction of an acrylamide with a 3-iodo-7-azaindole that is prepared through a domino coupling–cyclization sequence as a key step in a long linear synthesis consisting of four steps including isolation and purification operations.



Scheme 3 Retrosynthetic analyses of the transforming growth factor (TGF)-β1 antagonist SIS3 by Lautens

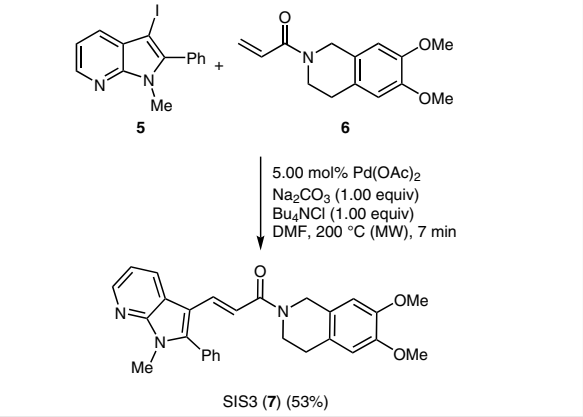
Therefore, we set out to extend the one-pot coupling–cyclization–alkylation synthesis of 1,2,5-trisubstituted 7-azaindoles by an iodination step embedded in the one-pot scenario. Deviating from the coupling–cyclization–alkylation protocol (see above), the iodination with *N*-iodosuccinimide was placed prior to the alkylation, taking advantage of the increased electron density of the anion resulting from the cyclization (Scheme 4).



Scheme 4 Four-component coupling–cyclization–iodination–alkylation synthesis of 3-iodo-1-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**5**)

After addition of methyliodide (**3b**) to the reaction mixture, the 3-iodo-1-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**5**) was isolated in 56% yield, which represents an average yield of 87% per bond-forming step. In comparison, from commercially available Boc-protected 2-amino pyridine Lautens' four-step synthesis of iodide **5** furnishes an overall yield of 38%, accounting for an average yield per step of 79%.

With iodide **5** in hand, acrylamide **6**[17] was reacted in a Heck reaction according to Lautens' conditions[15] to give, after purification, the transforming growth factor TGF-β1 antagonist SIS3 (**7**) in 53% yield (Scheme 5).



Scheme 5 Synthesis of the transforming growth factor TGF-β1 antagonist SIS3 (**7**)

In summary, we have disclosed a practical, efficient and rapid Pd-catalyzed one-pot coupling–cyclization–alkylation synthesis of 1,2,5-trisubstituted 7-azaindoles in the sense of a consecutive three-component fashion. The easy scalability of the sequence and its extension to a consecutive four-component coupling–cyclization–iodination–alkylation synthesis of 3-iodo-1-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine allowed a concise synthesis of SIS3 to be introduced; the latter is a selective TGF-β1 and signaling inhibitor that operates by suppressing Smad3 phosphorylation. Further studies applying the coupling–cyclization–alkylation concept to other heterocycles and its application in the syntheses of complex molecules are currently under way.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590837.

References and Notes

(1) Martinez-Outschoorn, U. E.; Peiris-Pages, M.; Pestell, R. G.; Sotgia, F.; Lisanti, M. P. *Nat. Rev. Clin. Oncol.* **2017**, *14*, 11.

(2) For selected reviews on privileged scaffolds and synthetic strategies, see for example: (a) Flick, A. C.; Ding, H. X.; Leverett, C. A.; Kyne, R. E.; Liu, K. K. C.; Fink, S. J.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2016**, *24*, 1937. (b) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347. (c) Davies, T. G.; Woodhead, S. J.; Collins, I. *Curr. Top. Med. Chem.* **2009**, *9*, 1705. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(3) (a) Rathi, A. K.; Syed, R.; Singh, V.; Shin, H. S.; Patel, R. V. *Recent Pat. Anti-Cancer Drug Discovery* **2017**, *12*, 55. (b) Asati, V.; Bharti, S. K.; Mahapatra, D. K.; Asati, V.; Budhwani, A. K. *Curr. Pharm. Des.* **2016**, *22*, 6039. (c) Blanco-Aparicio, C.; Carnero, A. *Biochem. Pharmacol.* **2013**, *85*, 629.

(4) For a review on various kinase inhibitors based upon azaindoles, see for example: Mérour, J.-Y.; Buron, F.; Ple, K.; Bonnet, P.; Routier, S. *Molecules* **2014**, *19*, 19935.

(5) For selected very recent examples, see for example: (a) Zhou, Q. Q.; Phoa, A. F.; Abbassi, R. H.; Hoque, M.; Reekie, T. A.; Font, J. S.; Ryan, R. M.; Stringer, B. W.; Day, B. W.; Johns, T. G.; Munoz, L.; Kassiou, M. *J. Med. Chem.* **2017**, *60*, 2052. (b) Feneyrolles, C.; Guiet, L.; Singer, M.; Van Hijfte, N.; Dayde-Cazals, B.; Fauvel, B.; Cheve, G.; Yasri, A. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 862. (c) Kim, J.; Moon, Y.; Hong, S. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5669. (d) Stanton, R. A.; Lu, X.; Detorio, M.; Montero, C.; Hammond, E. T.; Ehteshami, M.; Domaoal, R. A.; Nettles, J. H.; Feraud, M.; Schinazi, R. F. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4101. (e) Wucherer-Plietker, M.; Merkul, E.; Müller, T. J. J.; Esdar, C.; Knochel, T.; Heinrich, T.; Buchstaller, H. P.; Greiner, H.; Dorsch, D.; Finsinger, D.; Calderini, M.; Bruge, D.; Grädler, U. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3073. (f) Dayde-Cazals, B.; Fauvel, B.; Singer, M.; Feneyrolles, C.; Bestgen, B.; Gassiot, F.; Spenlinhauer, A.; Warnault, P.; Van Hijfte, N.; Borjini, N.; Cheve, G.; Yasri, A. *J. Med. Chem.* **2016**, *59*, 3886. (g) Liu, N.; Wang, Y. F.; Huang, G. C.; Ji, C. H.; Fan, W.; Li, H. T.; Cheng, Y.; Tian, H. Q.

Bioorg. Chem. **2016**, *65*, 146. (h) Baltus, C. B.; Jorda, R.; Marot, C.; Berka, K.; Bazgier, V.; Krystof, V.; Prie, G.; Viaud-Massuard, M. C. *Eur. J. Med. Chem.* **2016**, *108*, 701.

(6) For reviews, see for example: (a) Mérour, J.-Y.; Routier, S.; Suzenet, F.; Joseph, B. *Tetrahedron* **2013**, *69*, 4767. (b) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031.

(7) For selected reviews on strategic reaction design by multicomponent reactions, see for example: (a) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234. (c) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (d) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463. (e) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (f) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101.

(8) Müller, T. J. J. In *Multicomponent Reactions 1. General Discussion and Reactions Involving a Carbonyl Compound as Electrophilic Component, Science of Synthesis*; Müller, T. J. J., Ed.; Georg Thieme Verlag KG: Stuttgart, **2014**, 5.

(9) For one-pot and multicomponent accesses to 7-azaindoles, see: (a) Dongare, S. B.; Chavan, H. V.; Surwase, D. N.; Bhale, P. S.; Mule, Y. B.; Bandgar, B. P. *J. Chin. Chem. Soc. (Taipei)* **2016**, *63*, 323. (b) Dongare, S. B.; Chavan, H. V.; Bhale, P. S.; Mule, Y. B.; Kotmale, A. S.; Bandgar, B. P. *Chin. Chem. Lett.* **2016**, *27*, 99. (c) Vilches-Herrera, M.; Knepper, I.; de Souza, N.; Villinger, A.; Sosnovskikh, V. Y.; Iaroshenko, V. O. *ACS Comb. Sci.* **2012**, *14*, 434. (d) Suresh, R.; Muthusubramanian, S.; Senthilkumaran, R.; Manickam, G. *J. Org. Chem.* **2012**, *77*, 1468. (e) Tasch, B. O. A.; Merkul, E.; Müller, T. J. J. *Eur. J. Org. Chem.* **2011**, 4532. (f) Merkul, E.; Schäfer, E.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 3139. (g) Merkul, E.; Klukas, F.; Dorsch, D.; Grädler, U.; Greiner, H. E.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 5129. (h) Sharma, S. K.; Mandadapu, A. K.; Saifuddin, M.; Gupta, S.; Agarwal, P. K.; Mandwal, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2010**, *51*, 6022.

(10) Lessing, T.; Sterzenbach, F.; Müller, T. J. J. *Synlett* **2015**, *26*, 1217.

(11) (a) Kaupmees, K.; Trummal, A.; Leito, I. *Croat. Chem. Acta* **2014**, *87*, 385. (b) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

(12) Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, *62*, 4453.

(13) (a) Goerlich, J. R.; Schmutzler, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *102*, 211. (b) Beller, M.; Hein, M.; Tewari, A.; Zapf, A. *Synthesis* **2004**, 935.

(14) **Typical Procedure for the Synthesis of 1,5-Dimethyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (4b)**: In a dry screw-cap Schlenk tube with a magnetic stir bar were placed 2-amino-3-bromo-5-methyl pyridine (**1a**; 93 mg, 0.50 mmol), $Pd(PPh_3)_2Cl_2$ (9.0 mg, 13 µmol), and $(1\text{-Ad})_2PBn{\cdot}HBr$ (12 mg, 25 µmol) and the vessel was evacuated. After flushing the vessel with nitrogen, anhydrous DMSO (1.0 mL), the corresponding phenyl acetylene (**2a**; 61 mg, 0.60 mmol) and DBU (225 mg, 1.50 mmol) were added and the reaction mixture was stirred at 100 °C under nitrogen for 1 h until the bromide was completely consumed (reaction monitored by TLC). After cooling to rt KO*t*-Bu (253 mg, 2.25 mmol) and DMSO (0.50 mL) were added and the mixture was stirred at 100 °C under nitrogen for 0.25 h. After cooling to rt, methyliodide (**3b**; 142 mg, 1.00 mmol) was added to the reaction mixture, which was stirred at rt for 5 min. Then, deionized water or brine (20 mL) was added to the mixture. The aqueous layer was extracted several times with ethyl acetate or dichloromethane. The combined organic phases were dried (anhydrous sodium sulfate) and, after filtration, the solvents were removed in vacuo. The residue was adsorbed on silica and purified by chromatography on silica gel (SNAP cartridge 100 g, hexanes/ethyl acetate) with a Biotage SP-1 flash chromatography purification system to give analytically pure **4b** as a yellow solid. Yield: 72 mg (65%); mp 65 °C. IR (ATR): 3119 (w), 3078 (w), 3055 (w), 3005 (w), 2980 (w), 2945 (w), 2916 (w), 1599 (w), 1566 (w), 1532 (w), 1485 (m), 1296 (m), 748 (s), 694 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 3.86 (s, 3 H), 6.44 (s, 1 H), 7.42–7.52 (m, 5 H), 7.70–7.71 (m, 1 H), 8.19 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (CH_3), 30.1 (CH_3), 99.0 (CH), 120.7 (C_{quat}), 125.1 (C_{quat}), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.2 (CH), 132.6 (C_{quat}), 142.1 (C_{quat}), 143.5 (CH), 148.1 (C_{quat}). MS (EI, 70 eV): *m*/*z* (%) = 223 (15), 222 (100) $[M]^+$, 221 (84), 220 (5), 205 (6), 152 (5), 145 (17) $[M\text{-}C_6H_5]^+$, 111 (7), 110 (11). Anal. calcd. for $C_{15}H_{14}N_2$ (222.3): C 81.05, H 6.35, N 12.60; Found: C 80.92, H 6.07, N 12.40.

(15) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152.

(16) Jinnin, M.; Ihn, H.; Tamaki, K. *Mol. Pharmacol.* **2006**, *69*, 597.

(17) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem.* **2008**, *73*, 5859.