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New Opportunities with the Duff Reaction

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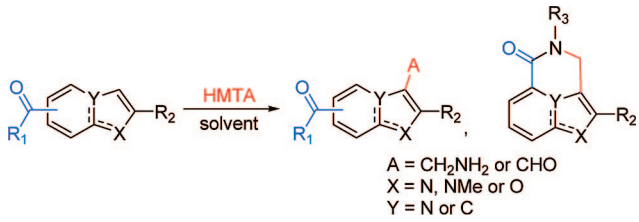
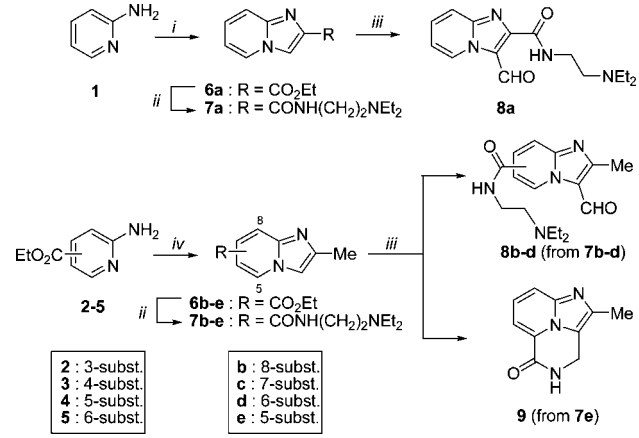


The Duff reaction (HMTA, AcOH or TFA) was studied on substituted [6 + 5] heterocyclic compounds. This reaction provides a useful route to aldehydes for compounds bearing sensitive amide functions. It gives also access to tricyclic lactams of potential biological interest. The formation of an aminomethyl intermediate in the Duff reaction mechanism is unequivocally demonstrated.

Formylation is a useful reaction in heterocyclic chemistry where it is widely used to gain access to multifunctional compounds. Several methods can be used to prepare heterocyclic formyl compounds. The Vilsmeier−Haack,[1] Reimer−Tiemann,[2] Gattermann,[3] and Rieche[4] reactions are commonly used in various heterocyclic systems, e.g., furan,[2b,3d] pyrrole,[2c] pyrimidine,[2e] indole,[1a–e,h,2g,4a–c] benzothiophene,[4e] etc.

In ongoing work to develop new antiproliferative drugs and melanoma tracers,[5] we set out to explore the formylation of imidazo[1,2-*a*]pyridinic compounds (IPs), substituted by an amidic chain at various core positions. Scheme 1 describes the synthesis of imidazopyridinic derivatives substituted on the C-2 or C-5−C-8 positions. Briefly, 2-aminopyridine compounds **1**−**5** reacted with the appropriate halo ketones to give ester-substituted IPs **6a**−**e** (50−63% isolated yields) by Tschitschibabin cyclization. Amides **7a**−**e** were then easily obtained with high yields (>90%) by direct amidification using trimethylaluminum as activator (Scheme 1).

SCHEME 1[a]



[a] Reagents and conditions: (i) $BrCH_2COCO_2Et$, EtOH, Δ; (ii) $NH_2(CH_2)_2NEt_2$, $AlMe_3$, THF, Δ; (iii) HMTA, AcOH, 90 °C; (iv) CH_3COCH_2Cl, EtOH, Δ.

Position 3 of the imidazo[1,2-*a*]pyridine ring is the most preferred position for electrophilic aromatic substitutions.[6] This position can be easily functionalized with a formyl group. The Vilsmeier−Haack reaction was generally considered to offer the best yields of formyl IP derivatives (around 30%),[6e] and this reaction is largely used in this series.[7] However, for amidic IP compounds **7a**−**e**, these conditions (like those of Riemer−Tiemann)

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(1) (a) Faust, R.; Garratt, P. J.; Trujillo Perez, M. A.; Piccio, V. J. D.; Madsen, C.; Stenstrom, A.; Frolund, B.; Davidson, K.; Teh, M. T.; Sugden, D. *Bioorg. Med. Chem.* **2007**, *15*, 4543. (b) Prueger, B.; Bach, T. *Synthesis* **2007**, *7*, 1103. (c) Kaufmann, D.; Pojarova, M.; Vogel, S.; Liebl, R.; Gastpar, R.; Gross, D.; Nishino, T.; Pfaller, T.; von Angerer, E. *Bioorg. Med. Chem.* **2007**, *15*, 5122. (d) Coldham, I.; Dobson, B. C.; Fletcher, S. R.; Franklin, A. I. *Eur. J. Org. Chem.* **2007**, *16*, 2676. (e) Coldham, I.; Dobson, B. C.; Franklin, A. I.; Fletcher, S. R. *Tetrahedron Lett.* **2007**, *48*, 873. (f) Nandhakumar, R.; Suresh, T.; Calistus Jude, A. L.; Rajesh Kannan, V.; Mohan, P. S. *Eur. J. Med. Chem.* **2007**, *42*, 1128. (g) Kolavi, G.; Hegde, V.; Khazia, I. A.; Gadadb, P. *Bioorg. Med. Chem.* **2006**, *14*, 3069. (h) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287. (i) Broggini, G.; Chiesa, K.; De Marchi, I.; Martinelli, M.; Pilati, T.; Zecchi, G. *Tetrahedron* **2005**, *61*, 3525.

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TABLE 1. Duff Reaction applied to IP Derivatives 7a−e

entry	substrate	chain position	reaction time	isolated yields[a] (%)
1	**7a**	2	2 h 30 min	**8a** (20)
2	**7b**	8	24 h	**8b** (41)
3	**7c**	7	24 h	**8c** (54)[b]
4	**7d**	6	24 h	**8d** (34)[c]
5	**7e**	5	2 h	**9** (44)

[a] Based on consumed starting material. [b] 40% of **7c** was recovered at the end of the reaction. [c] 30% of **7d** was recovered at the end of the reaction.

proved inefficient or offered only low yields of formyl compounds (degradation or yields below 10%, data not shown). Given these disappointing results, we decided to explore Duff formylation (hexamethylenetetramine (HMTA) in acetic acid[8] or TFA[9]), already used on several heterocyclic systems[10] and found to be efficient in IP series (18%[10a] to 29%[10b] isolated yield of formyl compounds).

Under TFA conditions, no reaction was observed and only starting material was recovered. In the presence of acetic acid, the Duff reaction led to acceptable yields (in IP series) of formyl compounds **8a−d** (Table 1, entries 1−4).

Unexpectedly, the Duff reaction conditions applied to **7e** afforded the *peri*-annulated compound **9**. This product was the result of an intramolecular *peri*-annelation reaction between the positions 3 and 5 of the IP nucleus. Reactions of *peri*-annelation had already been observed by ring closure using 3,5-bifunctionalized IP compounds[10a,11] and also directly obtained starting from 5-monofunctionalized IPs.[12]

Various concentrations of aqueous acetic acid were then studied. When acetic acid was concentrated (70% and above, Table 2, entries 2 and 3), only compound **9** was obtained in around 40% yield. With lower acid concentrations (Table 2, entries 4−6), *N*-alkylated compound **10** was also obtained. The overall reaction yield was highest in 30% aqueous acetic acid (Table 2, entry 4). Also, an increase in the pH of the medium lowered the yield of compound **9**. In water (Table 2, entry 7), the reaction was slower, as already observed,[13] but offered the highest ratio in favor of compound **10** (70% of compound **10**).

TABLE 2. Synthesis of Lactam Tricycles 9 and 10

entry	solvent	reaction time	pH	**9**[a] (%)	**10**[a] (%)
1	TFA			–[b]	
2	AcOH	2 h 30 min	2.51	44	
3	AcOH 70%	2 h 30 min	3.35	43	
4	AcOH 30%	2 h 30 min	3.82	37	24
5	AcOH 15%	2 h 30 min	4.21	29	28
6	AcOH 5%	2 h 30 min	4.73	22	28
7	H_2O	18 h	6.65	8	19

[a] Isolated yields. [b] Starting material was recovered.

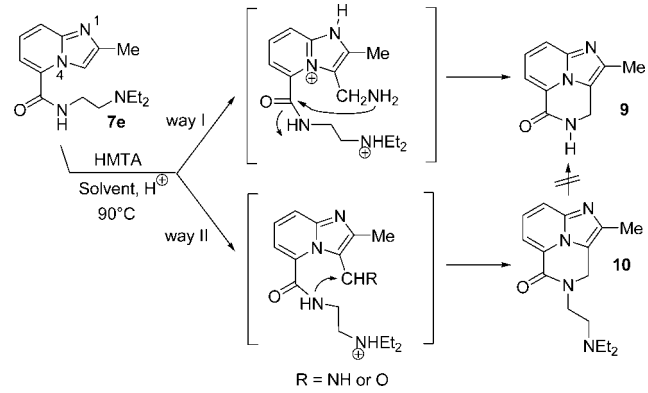

FIGURE 1. Proposed mechanisms for the formation of tricyclic lactams **9** and **10**.

To our knowledge, this is the first report of a Duff reaction without acid catalysis.

It has been assumed that the mechanism of the Duff reaction involves an aminomethylation (generated from HMTA) of the substrate,[13,14] followed by the dehydrogenation of the amine to the corresponding imine, which is hydrolyzed to give the formyl group.[8c,13,14] To investigate the formation of compound **9**, compound **10** was placed in the Duff conditions, but even after prolonged reaction time, no traces of compound **9** were detected and **10** was recovered. As **10** was not a precursor of **9**, two mechanisms seem to operate during the reaction (Figure 1).

In the more acidic conditions (Table 2, entries 2 and 3), the N-1 of the IP nucleus was largely protonated ($pK_a = 3.89$),[15] decreasing the electronic density of the amide carbonyl group and favoring attack by the aminomethyl group in position 3 to form the lactam cycle of compound **9** (Figure 1, path I). Faster attack of the amidic carbonyl by the nitrogen of the aminomethyl group than formation of the imine intermediate could explain this result.

In another run in AcOH, with an ethyl ester instead of the amidic chain in C-5 (compound **6e**), tricycle **9** was also obtained in 16% isolated yield (Scheme 2). This result unequivocally demonstrated the mechanism of formation of **9**: the nitrogen atom of the lactam cycle could only come from the aminomethyl group. Another run, with 30% AcOH, which offered best overall yields of lactams starting from **7e**, raised the yield of compound **9** (54% from **6e**).

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(15) The pK_a value was determined experimentaly by HCl (20 mM) titration of compound **7e**. The titration curve showed two pH jumps, the first one attributed to the tertiary amine protonation ($pK_a = 11.16$)[16] and the second one attributed to the protonation of the IP N-1[17] ($pK_a = 3.89$).

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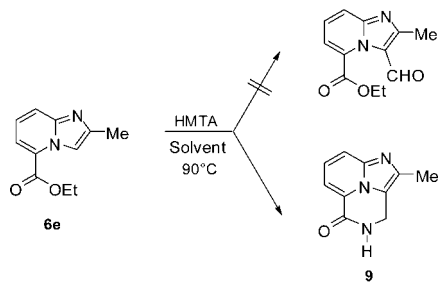
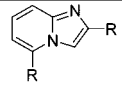
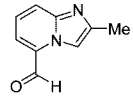
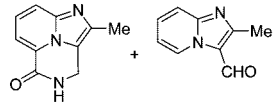
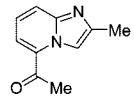
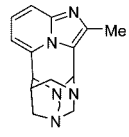
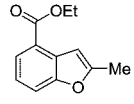
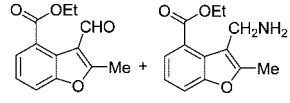
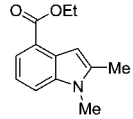
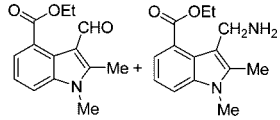
SCHEME 2



In less acidic media (30% aqueous acetic acid or lower, Table 2, entries 4−7), the pH of the medium entailed a lower degree of protonation of the IP nucleus N-1 and the nitrogen of the amide chain was thus less electron-depleted. The attack of the imine carbon (or the aldehyde carbon) by the amide nitrogen could then take place, giving tricyclic compound **10** (Figure 1, path II). When the pH was greater than about 3.5, a competition between the two routes was observed. The highest pH favored path II.

To study the scope of *peri*-annelation reactions, the Duff conditions (HMTA/AcOH) were extended to several compounds presenting different carbonyl groups in position 5 of the IP core. While the *peri*-annelation was observed with good yield with compounds **6e** and **7e**, the presence of a deactivating group (ester or amide) in position 2 of the IP nucleus (compounds **11** or **12**, Table 3, entry 1) opposed the electrophilic substitution in position 3 of the IP nucleus and the starting material was recovered. In the case of the aldehyde derivative **13** (Table 3, entry 2), marked degradation occurred. However, two compounds were isolated: tricyclic compound **9** and the 2-methyl-3-formylimidazo[1,2-*a*]pyridine **17**.[6e,18] This result can be explained by the oxidative conditions of the reaction.[19] The aldehyde group on position 5 can be converted into the acid intermediate, which gives tricyclic compound **9** by *peri*-annelation. Also, the acid can be decarboxylated and then followed the "classic" formylation reaction, leading to **17**.

TABLE 3. Duff Reaction Applied to Compounds 11−16

Entry	Starting materials[a]	Products (isolated yield)
1	 **11** : R = CO_2Et **12** : R = $CONH(CH_2)_2NEt_2$	-[b]
2	 **13**	 **9** (7%) + **17** (3%)
3	 **14**	 **18** (21%)
4[c]	 **15**	 **19** (32%) + **20** (16%)
5	 **16**	 **21** (6%) + **22** (14%)

[a] Compound **11** was synthesized according to the literature procedure.[11c] New compounds **12**−**16** were synthesized using classical methods (see the Supporting Information). [b] Starting material was recovered. [c] TFA was used instead of AcOH.

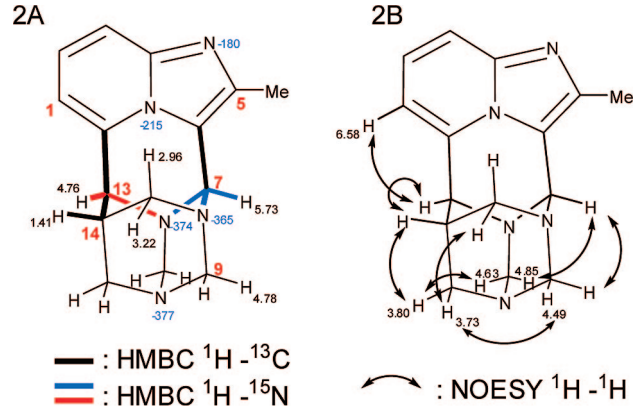


FIGURE 2. Structural assignment of compound **18**. Connectivities (bold lines) deduced from the COSY spectrum by key HMBC correlations and by selected NOESY (arrows).

In the case of the acetyl derivative **14** (Table 3, entry 3), the reaction led not to the expected formyl or lactam derivative but to compound **18**, which presented a more complex structure. The electronic impact mass spectrum of **18** presented a molecular ion at *m*/*z* 267. The analysis of the ^1H, ^{13}C NMR *J*-modulated and HSQC spectra indicated the presence of one methyl, four methylene, three aromatic, three nonaromatic methine, and four quaternary carbons. The $^1H-^{13}C$ HMBC analysis allowed the assignment of H-7 (5.73 ppm) and H-13 (4.76 ppm), Figure 2A. Also, the $^1H-^{15}N$ HMBC analysis allowed the assignment of the linkage of the carbon C-7 (70.8 ppm) with two nonaromatic nitrogens at δ −374 ppm and −365 ppm. In the same way, the carbon C-13 (59.8 ppm) was linked to the nitrogen at δ −374 ppm. Finally, the total assignment of the structure was achieved and the analysis of the $^1H-^1H$ NOESY analysis confirmed structure **18** (Figure 2B).

With this substrate, it seems that the presence of an enolizable function in position 5 of the IP nucleus completely modified reactivity toward HMTA. This novel reactivity requires a separate study.

The Duff reaction was also studied on 4-substituted indole or benzofuran nuclei. In the case of benzofuranic ester **15**, no Duff reaction occurred in AcOH. However, at TFA reflux, the corresponding formyl compound **19** was isolated, with 32% yield (Table 3, entry 4). This reaction also led to the formation of the aminomethyl derivative **20** (16% isolated yield). With the indole derivative **16**, formyl and aminomethyl derivatives (**21** and **22** respectively) were isolated (Table 3, entry 5). Once again, these results prove unequivocally that the aminomethyl derivative was an intermediate in the Duff mechanism. It seems that the cyclization of these two aminomethyl derivatives is inhibited by steric congestion around position 3 and no *peri*-

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(19) Potassium iodide was rapidly oxidized into iodine under the reaction conditions (HMTA, AcOH, 90 °C). Further addition of sodium thiosulfate decolorized the reaction medium.

annelation occurred. However, these compounds were tricyclic lactam precursors and could easily lead to the corresponding lactam derivatives, as described by Demerson et al.[20]

In summary, we studied the Duff reaction, to gain access to formyl amido-IP compounds. While Vilsmeier−Haack and Riemer-Tiemann conditions were not readily compatible with the amide chain, the Duff conditions were found to provide useful yields of formyl compounds. However, when the IP nucleus was substituted on position 5, no formylation was obtained, but a *peri*-annelation reaction occurred. This result proved unequivocally that the Duff reaction proceeded *via* an aminomethyl intermediate, isolated with compounds **20** and **22**. This *peri*-annelation reaction offers a new route to synthesize novel *peri*-fused tricyclic lactams, which have already been found to possess useful biological activities (anti-PDGFR,[21] polyADP(ribose) polymerase-1 inhibition,[22] central nervous system and antihypertensive activities).[20]

Experimental Section

General Procedure for the Duff Reaction. To a solution of 0.73 mmol of the appropriate compound in 5 mL of solvent (see Table 2) was added 200 mg of hexamethylenetetramine (1.43 mmol, 2 equiv). The solution was heated at 90 °C for the appropriate time (see Tables 1 and 2). After being cooled to rt, the solution was concentrated to around 2/3 volume and then 3 mL of water was added. The solution was basified with Na_2CO_3 to pH 8 and extracted twice with 25 mL of $CHCl_3$. The solution was dried on Na_2SO_4, filtered, and concentrated to dryness under reduced pressure and then purified by column chromatography.

2-Methyl-3,4-dihydro-1,4,8b-triazaacenaphthylen-5-one (9): purified on alumina, eluted by CH_2Cl_2/EtOH 98/2 (v/v); yield, see Table 2; yellow powder; mp 178−180 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 2.34 (s, 3H), 5.00 (s, 2H), 7.21 (t, 1H, J = 7.0 Hz), 7.36 (dd, 1H, J = 7.0 Hz, J = 1.0 Hz), 7.46 (dd, 1H, J = 7.0 Hz, J = 1.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 12.7 (CH_3), 39.9 (CH_2), 111.3 (C), 113.5 (CH), 120.0 (CH), 125.6 (CH), 126.8 (C), 138.3 (C), 143.4 (C), 160.4 (C); MS (EI, 70 eV) *m*/*z* (rel int) 187 (M^+, 51), 186 (100), 172 (11), 156 (8), 131 (8), 118 (8), 78 (19), 51 (22); HRMS *m*/*z* calcd for $C_{10}H_{10}N_3O$ ($M + H^+$) 188.0824, found 188.0806.

4-[2-(Diethylamino)ethyl)]-2-methyl-3,4-dihydro-1,4,8b-triazaacenaphthylen-5-one (10): purified on alumina, eluted by CH_2Cl_2/EtOH 98/2 (v/v); yield, see Table 2; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, 6H, J = 7.0 Hz), 2.32 (s, 3H), 2.54 (q, 4H, J = 7.0 Hz), 2.72 (t, 2H, J = 6.5 Hz), 3.60 (t, 2H, J = 6.5 Hz), 5.09 (s, 2H), 7.06 (dd, 1H, J = 7.0 Hz, J = 9.0 Hz), 7.43 (d, 1H, J = 9.0 Hz), 7.37 (d, 1H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9 (CH_3), 13.3 (CH_3), 46.1 (CH_2), 46.5 (CH_2), 47.3 (CH_2), 50.0 (CH_2), 108.6 (C), 112.2 (CH), 119.4 (CH), 123.7 (CH), 125.2 (C), 137.8 (C), 142.3 (C), 157.3 (C); MS (EI, 70 eV) *m*/*z* (rel int): 286 (M^+, 13), 187 (10), 186 (10), 86 (100), 58 (21); HRMS *m*/*z* calcd for $C_{16}H_{23}N_4O$ ($M + H^+$) 287.1872, found 287.1868.

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Supporting Information Available: Experimental details, characterizations, and a copy of ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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