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Preparation of 6-chloropyrazolo[3,4-*b*]pyridine-5-carbaldehydes by Vilsmeier–Haack reaction and its use in the synthesis of heterocyclic chalcones and dipyrazolopyridines

Jairo Quiroga [a,*], Yurina Diaz [a], Braulio Insuasty [a], Rodrigo Abonia [a], Manuel Nogueras [b,*], Justo Cobo [b]

[a] Heterocyclic Compounds Research Group, Department of Chemistry, Universidad del Valle, A. A. 25360 Cali, Colombia
[b] Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain

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ABSTRACT

Novel 6-chloropyrazolo[3,4-*b*]pyridine-5-carbaldehydes **5** have been synthesized from the 4,5-dihydropyrazolo[3,4-*b*]pyridine-6-ones **4** via Vilsmeier–Haack reaction. Further treatment of carbaldehydes **5** with acetophenones **6** and hydrazine hydrate afforded chalcone analogues **7** and dipyrazolo[3,4-*b*:4′,3′-*e*]pyridines **8**, respectively.

Pyrazolo[3,4-*b*]pyridine derivatives have been studied as antiviral[1] and potential antimalarial agents;[2] and some exhibit parasiticide properties[3] and bactericidal activity;[4] some others have been used as vasodilators[5] and evaluated for enzymatic inhibitory activity.[6]

The use of formylation reaction as synthetic strategy to form versatile carboxaldehyde intermediates is still of interest, due to both their intrinsic pharmacological properties and chemical reactivity.[7] Formylation reactions have been described for pyrazoles,[8] pyridines,[9] and pyrimidines,[10] as a key step to the introduction of functionalities via the intermediate carboxaldehydes, and further cyclization to fused heterocycles, such pyrido[2,3-*d*]pyrimidines,[11] pyrazolo[3,4-*b*]pyridines,[12] and pyrazolo[1,5-*a*]pyrimidines.[12]

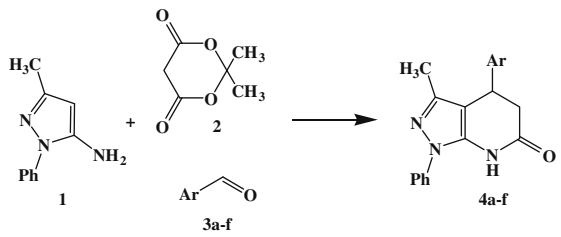
Vilsmeier–Haack reaction carried out on methylene-active compounds leads mainly to the formation of β-halo-carboxaldehyde derivatives, which are useful precursors in the construction of different heterocyclic compounds by means of numerous transformations.[12,13]

On the other hand, we have concentrated much of our recent work on the preparation of bioactive nitrogen-containing heterocycles, and have already described simple and efficient procedures to prepare interesting molecules with biological properties as pyrazolo[3,4-*b*]pyridin-6-ones **4a**–**f** in a three-component reaction from 5-amino-3-methyl-1-phenylpyrazole **1**, Meldrum's acid **2**, and aromatic aldehydes **3a**–**f** (Scheme 1).[14]

We describe here the preparation, 6-chloropyrazolo[3,4-*b*]pyridine-5-carbaldehydes **5**,[15] which have been proved as interesting precursors for new heterocyclic systems.

In this way, we have used as starting material the 4,5-dihydropyrazolo[3,4-*b*]pyridin-6-ones **4** and employing classical Vilsmeier–Haack conditions, we were able to prepare the desired 6-chloropyrazolo[3,4-*b*]pyridine-5-carbaldehydes **5** in moderate yields (Scheme 2).

These novel chloroformyl derivatives provide access to a great number of structures for the introduction of functionalities via the intermediate carbaldehydes. The Claisen–Schmidt condensation between heteroaromatic aldehydes and acetophenones is a synthetic tool for the generation of C–C bonds permitting the production of α,β-unsaturated ketones (chalcones).[16]



Scheme 1.

* Corresponding authors. Fax: +57 2 33392440 (J.Q.); +34 618907111 (M.N.).
E-mail addresses: jaiquir@univalle.edu.co (J. Quiroga), mmontiel@ujaen.es (M. Nogueras).

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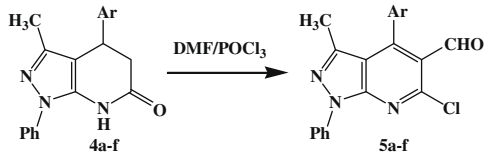
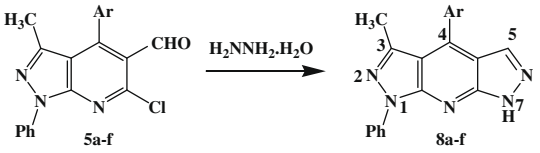


Comp.	Ar	m.p. (°C)	Yield %	m/z
5a	C_6H_5	165-167	55	347
5b	4-$CH_3C_6H_4$	173-175	45	361
5c	4-$CH_3OC_6H_4$	159-161	45	477
5d	4-ClC_6H_4	153-154	50	381
5e	4-BrC_6H_4	189-190	50	425
5f	4-$O_2NC_6H_4$	217-219	52	392

Scheme 2. Chorine-formylation of pyrazolopyridinones.



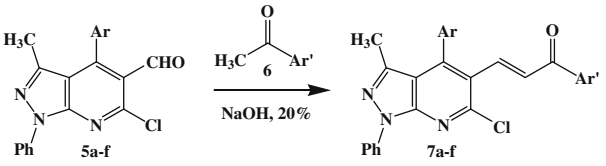
Comp.	Ar	m.p. (°C)	Yield %	m/z
8a	C_6H_5	232-233	70	325
8b	4-$CH_3C_6H_4$	258-260	68	339
8c	4-$CH_3OC_6H_4$	229-230	72	355
8d	4-ClC_6H_4	270-272	70	359
8e	4-BrC_6H_4	271-273	70	403
8f	4-$O_2NC_6H_4$	270-272	60	370

Scheme 4. Synthesis of dipyrazolopyridines.

The reaction of equimolar amounts of chloroaldehydes **5** with acetophenones **6** in ethanol with 10 drops of NaOH (20%) was stirred for 48 h at room temperature yielding the novel chalcone analogues **7a**–**l** (Scheme 3).[17]

On the other hand, due to the highly electron-deficient nature of the pyridine ring and the presence of the electron-withdrawing formyl group, the nucleophilic substitution of the adjacent chlorine atom can be favored; the nucleophilic heteroaromatic substitution (SNAr) allows us to introduce the hydrazino group that further cyclization leads to the formation of 1*H*,7*H*-dipyrazolo[3,4-*b*:4′,3′-*e*]pyridines **8a**–**f**. Accordingly, we carried out the reaction of equimolar amounts of aldehyde **5** with hydrazine hydrate in ethanol as a solvent (Scheme 4).[18] The synthesis of this kind of compounds has previously been reported by heating at 220–260 °C,[19a-d] and by microwave irradiation.[19e,f] Our approach allows to obtain unsymmetrically substituted dipyrazolopyridines bearing a free N–H bond which increases the possibility to introduce diversity by further selective transformations.

The structures of all new compounds were determined from analytical and spectral data, NMR 1D and 2D mainly, MS, and elemental analysis.



Comp.	Ar	Ar'	m.p. (°C)	Yield %	m/z
7a	C_6H_6	C_6H_6	>300	70	449
7b	C_6H_6	*p*-OCH_3-Ph	>300 (d)	75	479
7c	C_6H_6	*p*-Cl-Ph	>300 (d)	80	483
7d	*p*-OCH_3-Ph	C_6H_6	250 (d)	75	479
7e	*p*-OCH_3-Ph	*p*-Cl-Ph	300 (d)	70	513
7f	*p*-Cl-Ph	*p*-OCH_3-Ph	>300	75	513
7g	*p*-Cl-Ph	*p*-Cl-Ph	280 (d)	85	517
7h	*p*-Cl-Ph	*p*-Br-Ph	>300	85	561
7i	*p*-Br-Ph	*p*-Cl-Ph	>290 (d)	85	561
7j	*p*-Br-Ph	*p*-NO_2-Ph	>300	70	572
7k	*p*-NO_2-Ph	C_6H_6	>250 (d)	75	494
7l	*p*-NO_2-Ph	*p*-OCH_3-Ph	248 (d)	80	524

Scheme 3. Synthesis of heterocyclic analogues of chalcones.

In conclusion, we have described the preparation of novel 6-chloro-3-methyl-l-phenylpyrazolo[3,4-*b*]pyridine-5-carbaldehydes as versatile precursors for diverse pyrazolopyridine derivatives. These new compounds present a privileged core from a biological point of view. The chemical and biological interest of the pyrazolopyridinecarbaldehydes and bis-pyrazolopyridines mainly obtained in these experiments are under investigation.

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15. *4-Aryl-6-chloro-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbaldehydes* **5a–f**. To a suspension of *4-aryl-4,5-dihydro-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6(7H)-one* **4** (1 mmol) in DMF (2 mL) cooled into an ice/water bath, $POCl_3$ (0.2 mL, 2.1 mmol) was added dropwise, and afterwards the reaction mixture was stirred for 30 min at ambient temperature, and finally heated at 100 °C for 5 h. After cooling down to ambient temperature, ice was added and the mixture was neutralized with sodium bicarbonate with vigorous stirring. The yellow precipitate was filtered, dried, and recrystallized from DMF. Data for 6-chloro-4-(4-chlorophenyl)-3-methyl-l-phenylpyrazolo[3,4-*b*]pyridine-5-carbaldehyde **5d**: Yellow solid, mp 153–154 °C (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.00 (CH_3), 7.27 (d, 2H, $H_{o'}$ J = 8.3 Hz), 7.36 (t, 1H, H_p J = 7.9 Hz, NPh), 7.53 (m, 4H, $H_{m'}$, H_m), 8.20 (d, 2H, H_o J = 7.9 Hz, NPh), 10.32 (s, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.4 (CH_3), 115.4 (C3a), 121.2 (C5), 121.3 (C_o NPh) 126.8 (C_p NPh), 128.7 (C_m NPh), 129.2 ($C_{m'}$), 128.6 (C7), 129.6 ($C_{o'}$), 132.2 ($C_{p'}$), 135.4 ($C_{i'}$), 138.2 (C_i NPh), 145.2 (C6), 148.8 (C3), 149.8 (C4), 152.1 (C7a), 188.9 (CHO). EI MS: *m*/*z*: 385/383/381 (M^++4/M^++2/M^+, 12/69/100), 346 (14, M^+−Cl), 241 (18), 77 (18). HR-MS (EI) calcd for $C_{20}H_{13}Cl_2N_3O$, 381.0436, found 381.0449. Anal. Calcd for $C_{20}H_{13}Cl_2N_3O$: C, 62.84; H, 3.43; N, 10.99. found: C, 63.00; H, 3.43; N, 10.91.
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17. *2(E)-3-[4-Aryl-6-chloro-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-5-yl]-1-aryl-2-propen-1-ones* **7a–l**. A solution of compound **5** (1 mmol) and the corresponding acetophenones **6** (1 mmol) in ethanol with 10 drops of NaOH (20%) was stirred for 48 h at rt. The solid product was collected, washed with ethanol, and recrystallized from ethanol. Data for 2(*E*)-3-[6-chloro-4-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1-(4-methoxyphenyl)-2-propen-1-one **7f**: Yellow solid, mp >300 °C (dec) (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.04 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 6.90 (d, 1H, H-9, J = 16 Hz), 6.91 (d, 2H, $H_{m''}$, J = 8.6 Hz), 7.34 (m, 3H, $H_{o'}$, H_p), 7.52 (d, 2H, $H_{m'}$, J = 7.6 Hz), 7.57 (d, 2H, H_m NPh, J = 8.3 Hz), 7.63 (d, 2H, $H_{o''}$, J = 8.6 Hz), 7.77 (d, 1H, H-8, J = 16 Hz), 8.22 (d, 2H, H_o NPh, J = 8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.5 (CH_3), 55.4 (OCH_3), 113.9 ($C_{o''}$–$C_{m'}$), 115.1 (C3a), 120.9 (C_o), 122.5 (C5), 126.3 (C_p), 122.2 (C_m), 129.8 (C9), 120.46 ($C_{m'}$), 120.7 ($C_{o'}$), 164.0 ($C_{p'}$), 135.4 ($C_{i'}$), 137.1 (C8), 138.7 (C_i), 143 (C6), 145.9 (C3), 148.1 (C4), 151.0 (C7a), 163.6 ($C_{p'}$), 187.8 (CHO). EI MS: *m*/*z*: 517/515/513 (M^+, 10), 480/478 (35/100, M^+−Cl), 77 (8). Anal. Calcd for $C_{29}H_{21}Cl_2N_3O_2$: C, 67.71; H, 4.11; N, 8.17. Found: C, 67.60; H, 4.23; N, 8.09.
18. *4-Aryl-3methyl-1-phenyl-1H,7H-dipyrazolo[3,4-b:4′,3′-e]pyridines* **8a–f**. A solution of compound **5** (0.2 mmol) and an excess of hydrazine monohydrate (0.5 mL) in ethanol (5 mL) was heated under reflux for 75 min, then allowed to cool down to ambient temperature. The solid product was collected, washed with ethanol, and recrystallized from ethanol. Data for 4-(4-chlorophenyl)-3-methyl-l-phenyl-1*H*,7*H*-dipyrazolo[3,4-*b*:4′,3′-*e*]pyridine **8d**: Yellow solid, mp 270–272 °C (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.17 (CH_3), 7.28 (t, 1H, H_p NPh J = 7.5 Hz), 7.53 (t, 2H, H_m NPh J = 7.5 Hz), 7.56 (d, 2H, $H_{o'}$ J = 8.5 Hz), 7.70 (d, 2H, $H_{m'}$ J = 8.5 Hz) 7.99 (s, 1H, H5), 8.26 (d, 2H, H_o NPh J = 7.6 Hz) 13.62 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 15.9 (CH_3), 112.3 (C3a), 113.1(C4a), 120.5 (C_o NPh), 125.6 (C_p NPh), 129.1 ($C_{o'}$) 129.1 ($C_{o'}$), 129.5 (C_m NPh), 131.9 ($C_{m'}$), 133.2 ($C_{i'}$), 134.2 (C5), 134.8 ($C_{p'}$), 139.1 (C4), 139.6 (C_i), 143.9 (C3), 151.4 (C8a), 152.2(C7a). EI MS: *m*/*z*: 361/359 (M^++2/M^+, 36/100), 77 (7). Anal. Calcd for $C_{20}H_{14}ClN_5$: C, 65.13; H, 4.10; N, 18.99. Found: C, 65.08; H, 3.92; N, 18.94.
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