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Synthesis of carbamoylpyridine and imidazo[1,5-*a*]pyridin-1,3-diones via *ortho*-acetalhydantoin intermediates

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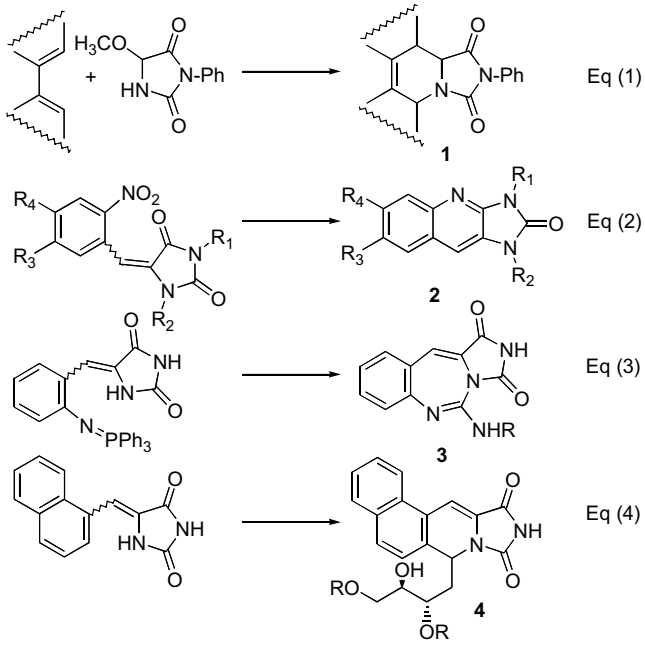
Abstract—A new method for preparing carbamoylpyridine and imidazo[1,5-*a*]pyridin-1,3-dione rings from an *ortho*-acetalmethylideneimidazolidin-2,4-dione is described.

1. Results and discussion

Several 5-substituted hydantoins display a wide range of biological properties,[1] and have proved to be useful precursors of α-amino acids after alkaline hydrolytic degradation[2] or enzymatic reactions.[3] Different approaches have been used for the construction of pyridine (or diazepine) moieties. 5-Substituted hydantoins have been found to be valuable precursors of a great variety of heterocyclic systems: 5-methoxy-3-phenylhydantoin reacts with various conjugated dienes to give Diels–Alder-type adducts **1**[4] (Scheme 1, Eq. 1).

More recently 5-(2-nitrophenylmethylidene)imidazolidin-2,4-dione derivatives have been synthesized as key intermediates for access to imidazo[4,5-*b*]quinolin-2-ones **2** after reduction by 10% Pd/C followed by acid-catalyzed ring closure (Eq. 2).[5] This reactivity was extended by Molina[6] with 5-(2-(triphenylphosphoranylidene)phenyl)methylidenehydantoin to afford imidazo[1,5-*c*][1,3]benzodiazepines **3** via an aza-Wittig/carbodiimide mediated annulation process (Eq. 3). Alternatively, by-product **4** has been observed when a trimethylsilylnucleoside is condensed with 5-(naphthylmethylidene)imidazolidin-2,4-dione[7] (Eq. 4).



Scheme 1.

Further to our previous work on the heterocyclization of aromatic rings[8] we report a new protocol for the synthesis of imidazo[1,5-*a*]pyridine moieties based on the nucleophilic attack of the more basic[9] *N*-1 hydantoin ring on an *ortho*-carbaldehyde function (Scheme 2).

Keywords: Hydantoin; Imidazolidin-2,4-dione; Imidazo[1,5-*a*]pyridin-1,3-dione; Carbamoylpyridine.
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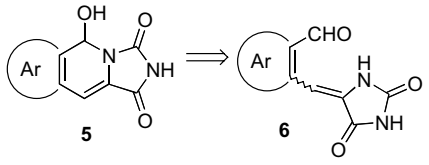


Scheme 2.

First we examined the reactivity of an imidazo[1,2-*a*]-pyridine series. The most convenient route to 5-(2-formylimidazo[1,2-*a*]pyridin-3-yl)methylideneimidazolidin-2,4-dione **6a** appeared to involve a Horner–Wadsworth–Emmons type olefin-forming reaction between diethyl 2,4-dioxoimidazolidine-5-phosphonate and **8a** followed by acidic deprotection (Scheme 3). The required compound **8a** was prepared from 3-bromo-2-diethoxymethylimidazo[1,2-*a*]pyridine **7a** by a reported procedure.[10]

Compound **9a** was obtained from **8a** using Meanwell's procedure[11] in 45% yield. Our attempts to hydrolyze the ketal moiety using catalytic concentrated HCl in CH_3CN/H_2O (3/1, v/v)[12] gave the unexpected amide **10a** in 80% yield and not the predicted aldehyde **6a**, as shown in Scheme 3. This surprising pyridinization reaction can be explained by deprotection of **9a**, followed by intramolecular cyclization to give the imidazo[1,5-*a*]pyridine intermediate **5a**. Once intermediate **5a** is formed, it can be converted into **10a** after dehydration, hydrolysis and finaly decarboxylation. The mechanistic details are set out in Scheme 4.

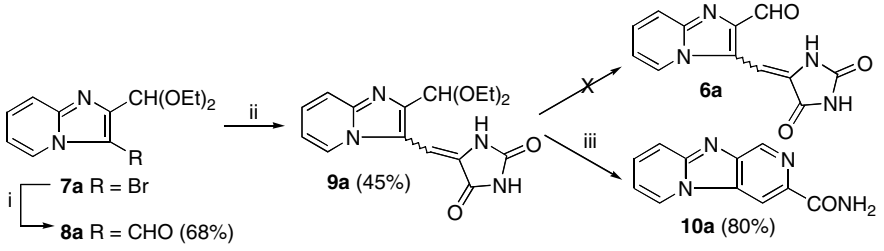
To explore the potential applications of this method, we set out to generalize the protocol. A wide variety of aromatic rings possessing acetal and bromo groups in the *ortho* position were chosen as starting materials. The reactions and results are summarized in Table 1.

Acetal aldehydes **8b–f** were easily prepared by lithiation of bromoacetals **7b–f**[13,18] with *n*-BuLi at −70 °C and subsequent treatment with DMF[19] (Table 1, entries 1–5). Addition of aromatic aldehydes **8b–f** to a slight excess of diethyl 2,4-dioxoimidazolidine-5-phosphonate[20] and sodium ethoxide in ethanol at room temperature gave a mixture of (*E*)- and (*Z*)-5-arylidenehydantoins **9b–f**.[21]

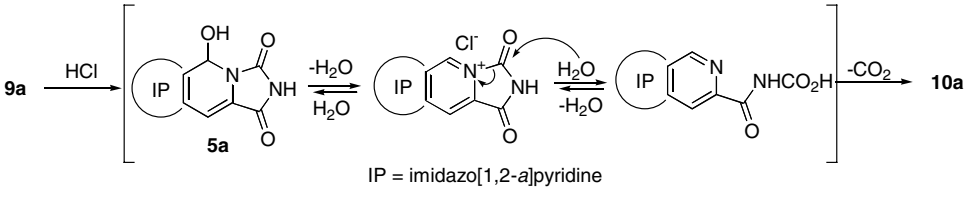
Under the hydrolysis conditions used previously for **9a**, the pyridine hydantoins gave the stable imidazo[1,5-*a*]pyridinic compounds **5b**,**c** in 45% and 87% yields, respectively (Table 1, entries 1, 2). This direct deprotection/cyclization reaction agrees with the mechanism proposed in Scheme 4. The use of phenyl, naphthalene, or indole units afforded amides **10b–d** in excellent yields (Table 1, entries 3–5). Similar observations have been reported for related structures.[22] Compounds **5b**,**c** and **10b–d** were characterized by ^1H, ^{13}C and mass spectroscopy.[12]

In order to obtain imidazo[1,5-*a*]pyridin-1,3-dione **5d** from acetal **9d**, milder conditions (catalytic AcOH) were investigated. However no reaction took place at room temperature and only formation of **10b** was observed at 50 °C. Therefore, our attention was focused on conversion of imidazonaphthyridines **5b**,**c** to the corresponding amides. Attempts to hydrolyze **5b**,**c** under more acidic conditions CH_3CN/HCl concd (3/1, v/v) at room temperature or reflux gave only starting materials. Presumably, the presence of a second pyridine moiety increases the stability of hydroxyimidazonaphthyridines **5b**,**c**.

In conclusion, this procedure offers a new, simple, and attractive method for the synthesis of carbamoylpyridine or imidazo[1,5-*a*]pyridin-2,4-dione cores in a one-pot synthesis from *ortho*-acetalmethylidenehydantoins.

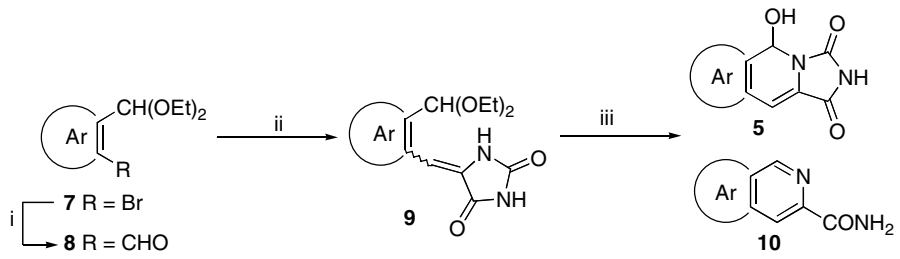


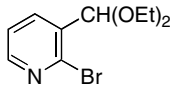
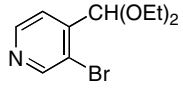
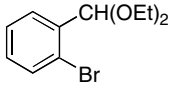
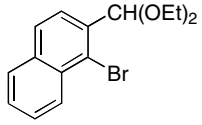
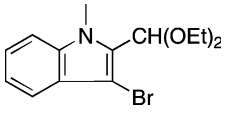
Scheme 3. Reagents and conditions: (i) 1/*n*-BuLi, THF, −60 °C, 2/DMF, rt; (ii) diethyl 2,4-dioxo imidazolidin-5-phosphonate, EtONa; (iii) CH_3CN/H_2O (3/1, v/v), concd HCl (three drops).



Scheme 4.

Table 1. Cyclization of arylidenehydantoins[a]



Entry	Starting material	Yield (%)		
		Acetaldehyde[b]	Hydantoin	Product
1	 **7b**[13]	**8b**[14] (42)	**9b** (46)	**5b** (45)
2	 **7c**[13]	**8c**[15] (68)	**9c** (65)	**5c** (87)
3	 **7d**	**8d**[16] (68)	**9d** (67)	**10b**[17] (81)
4	 **7e**[18]	**8e** (51)	**9e** (74)	**10c** (83)
5	 **7f**[13]	**8f** (54)	**9f** (15)	**10d** (43)

Reagents and conditions: (i) 1/*n*-BuLi, THF, −70 °C, 2/DMF, rt; (ii) diethyl 2,4-dioxo imidazolidin 5-phosphonate, EtONa; (iii) CH_3CN/H_2O (3/1, v/v), concd HCl (three drops).

[a] All products were characterized by IR, NMR and mass spectroscopy.

[b] Isolated yields after column chromatography.

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Dechambre, C.; Canitrot, D.; Blache, Y.; Lartigue, C.; Chavignon, O.; Teulade, J. C. *Heterocycles* **2002**, *57*, 21–38.
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11. Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K. *J. Org. Chem.* **1991**, *56*, 6897–6904.
12. Typical procedure for hydrolysis: To a solution of **9** (2.91 mmol) in 40 mL of CH_3CN/H_2O (3/1, v/v) was added a small quantity of concentrated HCl (three drops). The solution was stirred at room temperature. For compounds **9a**,**d**–**f** the solution was made basic with Na_2CO_3 (1.00 g, 9.43 mmol) and extracted with CH_2Cl_2 (3×20 mL). The extract was dried (Na_2SO_4) and evaporated to give a yellow precipitate. The product was washed with ether (5 mL) to give **10a**–**d**. For compounds **9b**,**c** the precipitate was collected by filtration and dried under vacuum to afford **5b**,**c**.
Compound **5b**: mp: 168–170 °C; ^{1}H (400 MHz, DMSO-d_6) δ 6.63 (d, 1H, $J = 8$ Hz), 6.73 (s, 1H), 7.15 (d, 1H, $J = 8$ Hz), 7.46 (dd, 1H, $J = 4.5$, 7.5 Hz), 7.94 (d, 1H, $J = 7.5$ Hz), 8.66 (d, 1H, $J = 4.5$ Hz), 11.74 (br s, 1H); ^{13}C (100 MHz, DMSO-d_6) δ 71.9, 105.5, 123.4, 128.5, 131.5, 136.4, 147.4, 150.3, 153.3, 162.5; MS *m*/*z* 217 (M^+, 9), 199 (34), 157 (68), 129 (100), 102 (30), 75 (19), 63 (20), 51 (25).
Compound **5c**: mp: 216–218 °C; ^{1}H (400 MHz, DMSO-d_6) δ 5.12 (br s, 1H), 6.79 (s, 1H), 7.09 (s, 1H), 8.12 (d, 1H, $J = 5.5$ Hz), 8.90 (d, 1H, $J = 5.5$ Hz), 9.17 (s, 1H), 11.99 (s, 1H); ^{13}C (100 MHz, DMSO-d_6) δ 70.4, 99.8, 125.8, 127.5, 131.0, 141.7, 141.8, 145.5, 153.3, 162.1; MS m/z 217 (M^+, 12), 199 (45), 157 (66), 129 (100), 102 (17), 75 (30), 51 (23).
Compound **10a**: 245–247 °C; ^{1}H (400 MHz, DMSO-d_6) δ 7.17 (t, 1H, $J = 7$ Hz), 7.67 (br s, 1H), 7.75 (m, 1H), 7.83 (d, 1H, $J = 9$ Hz), 8.24 (br s, 1H), 9.13 (s, 1H), 9.19 (s, 1H), 9.36 (d, 1H, $J = 7$ Hz); ^{13}C (100 MHz, DMSO-d_6) 106.9, 112.0, 117.7, 128.5, 132.9, 134.9, 140.5, 141.0, 142.1, 150.0, 166.4; MS m/z 212 (M^+, 36), 169 (56), 141 (12), 78 (100), 51 (91).
Compound **10c**: mp: 275–277 °C; ^{1}H (400 MHz, DMSO-d_6) δ 7.57 (br s, 1H), 7.63 (m, 2H), 7.91 (m, 3H), 8.12 (br s, 1H), 8.74 (m, 1H), 9.07 (s, 1H), 9.16 (s, 1H); ^{13}C (100 MHz, DMSO-d_6) 116.6, 125.5, 126.2, 129.6, 129.7, 129.9, 130.6, 131.1, 131.6, 134.9, 136.2, 147.8, 152.4, 168.0; MS m/z 222 (M^+, 62), 179 (100), 151 (35).
Compound **10d**: 223–225 °C; ^{1}H (400 MHz, DMSO-d_6) δ 4.03 (s, 3H), 7.34 (t, 1H, $J = 8$ Hz), 7.50 (br s, 1H), 7.67 (t, 1H, $J = 8$ Hz), 7.74 (d, 1H, $J = 8$ Hz), 8.10 (br s, 1H), 8.41 (d, 1H, $J = 8$ Hz), 8.87 (s, 1H), 9.03 (s, 1H); ^{13}C (100 MHz, DMSO-d_6) 26.5, 110.3, 113.8, 120.1, 120.6, 122.2, 127.7, 128.6, 130.9, 137.7, 140.1, 141.8, 166.9; MS m/z 225 (M^+, 100), 182 (95), 181 (85), 127 (18).
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19. Typical procedure for the preparation of aldehydes **8b**–**f**: *n*-BuLi (4.26 mL of an 1.6 M hexane solution, 6.81 mmol) was added dropwise, under argon, to a stirred solution of the appropriate acetal bromide **7** (6.19 mmol) in THF (16 mL) at −70 °C. After 30 min, DMF (5.7 mL, 73.4 mmol) was added slowly dropwise keeping the temperature at −70 °C and stirring continued for 30 min. The solution mixture was cooled to room temperature, stirred for 30 min, poured into aqueous saturated ammonium chloride solution (100 mL), and extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography Al_2O_3/CH_2Cl_2 for **8d**,**f**, Al_2O_3/AcOEt/hexanes (1/9, v/v) for **8e**, SiO_2/AcOEt/hexanes (8/2, v/v) for **8b**, and SiO_2/AcOEt/CH_2Cl_2 (9/1, v/v) for **8c**. All these compounds were accompanied by the corresponding dehalogenated compounds.
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21. Typical procedure for the preparation of 5-arylidenehydantoin **9**: To a solution of sodium (0.18 g, 7.82 mmol) in anhydrous ethanol (15 mL) was added, under argon, diethyl 2,4-dioxoimidazolidine-5-phosphonate (1.10 g, 4.66 mmol) and the appropriate aldehyde **8** (3.10 mmol). The solution was stirred at room temperature for 4 h then diluted with water (30 mL). The yellow precipitate was collected via filtration, washed with cold ethanol (10 mL), and dried under reduced pressure to give **9**. The hydantoins **9** were generally isolated as mixtures of geometrical isomers.
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