Acetic Anhydride Generated Imidazolium Ylide in Ring Closures onto Carboxylic Acids; Part of the Synthesis of New Potential Bioreductive Antitumor Agents

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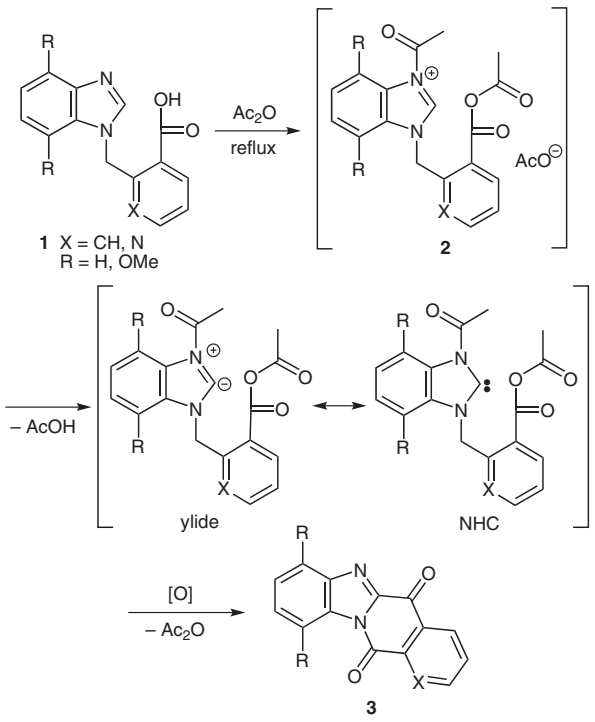
Abstract: Acetic anhydride behaves as a traceless activating agent allowing thermal intramolecular condensation of 2-(benzimidazol-1-ylmethyl) benzoic and nicotinic acids. Autoxidation gives benzimidazo[1,2-*b*]isoquinoline-6,11-diones (intermediates characterized) and benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-diones in a facile, one-pot transformation. The 1,4-dimethoxy analogue of the former is converted into benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone using cerium ammonium nitrate (CAN). The 1,7-naphthyridine-5,12-dione system readily ring-opens, and an X-ray crystal structure of the methanol adduct was obtained.

Key words: benzimidazoles, condensation, heterocycles, quinones, ylides

1,3-Dialkylated imidazolium salts are weakly acidic and will readily form an imidazolium ylide species that is isoelectronic with the imidazolin-2-ylidene (N-heterocyclic carbene, NHC).[1] The electron-rich (nucleophilic) nature of the singlet NHC has led to its use in a wide-range of applications in transition-metal-catalyzed and organocatalyzed reactions (including benzoin condensation and acyl transfer).[2] Moreover, the reactive intermediates have been used to trap electrophiles and to functionalize imidazoles at the 2-position.[3,4] In 1977, seminal work by Regel and Büchel established substitution of ketone and ester functionality onto the 2-position of imidazole (and benzimidazole) using imidazolium ylide species.[5,6] These reactions used various acid chlorides or chloroformic esters in the presence of triethylamine in polar solvents. Some years later, the protocol was used in the regioselective acylation of the electron-deficient position of imidazopyridines using benzoyl chloride under thermal or triethylamine-mediated conditions.[7] Imidazole (and benzimidazole) reacted with phthaloyl dichlorides in the presence of triethylamine to give imidazo[1,2-*b*]isoquinolinediones,[5,8] and an ylide intermediate was proposed.[5]

Considering these reported reactions, we have devised a facile new method for annulation directly onto a carboxylic acid using acetic anhydride (Ac_2O) under reflux. Ac_2O is the solvent with a dual role of mediating the in situ formation of the reactive intermediates and the derived leaving group from carboxylic acid **1** (Scheme 1). Deprotonation at the 2-position of the imidazole of salt **2** occurs thermally, possibly via the acetate counter ion (releasing AcOH). The ylide and NHC are then primed for six-membered annulation, and the required aromatic diones **3** form upon autoxidation of *N*-benzyl methylene intermediates. The synthesis is part of ongoing research in our group to screen bioreductive antitumor agents.[9,10] The alicyclic ring-fused diones **3** and (benzimidazole)quinone derivatives are expected to be bioactivated through reduction at the *para*-dione moieties prior to a cellular cytotoxic response.



Scheme 1 Proposed mechanism for intramolecular condensation of (benzimidazol-1-ylmethyl) benzoic and nicotinic acids

Carboxylic acids **1a–d** were prepared in two synthetic steps: alkylation in the presence of NaH in *N*,*N*-dimethylformamide (DMF), and base-mediated hydrolysis of the methyl ester adducts, which proceeded in yields of 71–77 and 80–91%, respectively (Scheme 2). Benzimidazole and 4,7-dimethoxybenzimidazole reacted with methyl 2-(bromomethyl)benzoate (**4**) to form methyl esters **7a** and **7c**, respectively, which were hydrolyzed to give 2-(benzimidazol-1-ylmethyl)benzoic acids **1a** and **1c**. Methyl 2-

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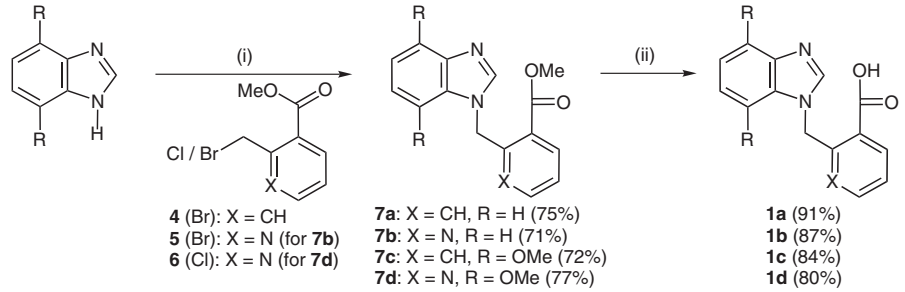
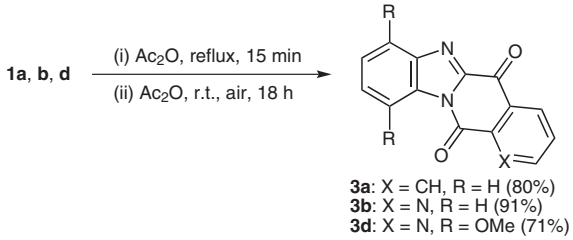


Scheme 2 Preparation of carboxylic acids. *Reagents and conditions*: (i) NaH, DMF, then **4**, 80 °C, 1 h for **7a** and **7c**; or **5**, r.t., 18 h for **7b**; or **6**, 80 °C, 18 h for **7d**; (ii) NaOH (0.8 M), MeOH, r.t., 18 h.

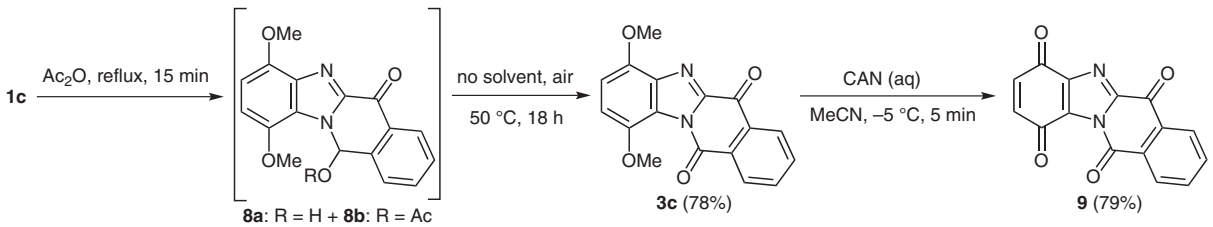
(bromomethyl)nicotinate (**5**) and methyl 2-(chloromethyl)nicotinate (**6**) were used to respectively alkylate benzimidazole and 4,7-dimethoxybenzimidazole to give methyl esters **7b** and **7d**, which were hydrolyzed to 2-(benzimidazol-1-ylmethyl)nicotinic acids **1b** and **1d**.

Annulations[11] via the proposed reactive intermediates required heating carboxylic acids **1a–d** in acetic anhydride under reflux for 15 minutes. TLC (except for **1c**) indicated complete consumption of acids, and the generation of a complex mixture of products. After overnight stirring in Ac_2O at room temperature, benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**3a**) was isolated in 80% yield, and benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-diones **3b** and **3d** were isolated in 91 and 71% yield, respectively (Scheme 3). The crude reaction mixture of **1c** was evaporated after the initial reflux, and part of the residue was purified by chromatography to yield the unstable autoxidation alcohol **8a** (which slowly converted into **3c**) and acetate derivative **8b** (Scheme 4).[12] It was not possible to isolate and characterize the non-oxidized cyclized adduct by attempted exclusion of air. Purified intermediates **8a** and **8b** were combined with the derived residue, and converted into the required dione **3c** in 78% yield (from **1c**) upon further heating in air at 50 °C for 18 hours. It should be noted that methyl esters **7a–d** remained unchanged when heated in acetic anhydride or acetic acid under reflux for prolonged times, and no annulations were observed when acetic anhydride was replaced by acetic acid under reflux for **1a–d**.

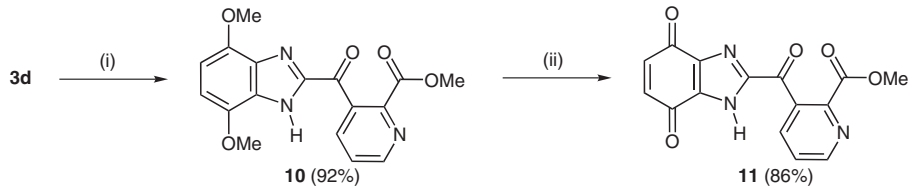


Scheme 3 Acetic anhydride mediated annulations

Cerium (IV) ammonium nitrate (CAN) was found to readily convert **3c** into the target tetrone **9** in 79% yield (Scheme 4),[13] although under the same conditions no isolable products were obtained from **3d**. We presume that the more reactive benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione system was hydrolytically ring-opened during the attempted oxidations. This proposal was supported by the isolation of the ring-opened adduct **10** in 92% yield when **3d** was stirred in methanol (Scheme 5). X-ray crystallographic analysis confirmed the structure of **10** (Figure 1),[14] with the site of opening analogous to that reported for **3a**.[8] The dimethoxy-substituted compound **10** was then readily converted into the corresponding benzimidazolequinone **11**[15] in 86% yield using CAN.



Scheme 4 Isolation of annulation intermediates followed by formation of the target tetrone



Scheme 5 Ring-opening of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione. *Reagents and conditions*: (i) MeOH, r.t. 18 h; (ii) CAN (aq), MeCN, –5 °C, 5 min.

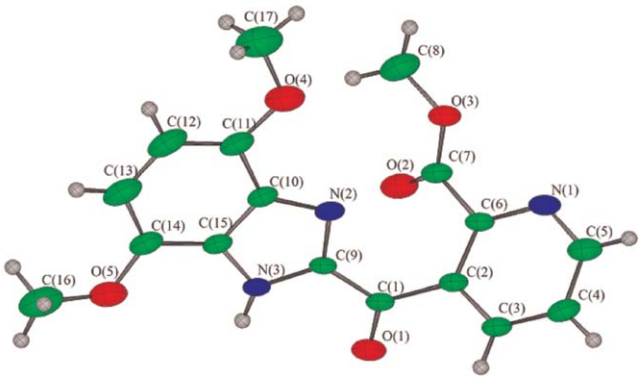


Figure 1 X-ray crystal structure of **10**

In conclusion, a facile protocol for the formation of benzimidazo[1,2-*b*]isoquinoline-6,11-diones, and benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-diones from carboxylic acids using only Ac_2O, and studies on the transformation of adducts into quinones have been carried out. Compounds **3a–d**, **9** and **11** are currently undergoing cyclic voltammetry and antitumor evaluation.[9,10]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are a detailed experimental section and NMR spectra.

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(11) **General Procedure for Annulation**: Carboxylic acid **1a–d** (0.79 mmol) in Ac_2O (50 mL) was heated under reflux for 15 min. The mixture was stirred at r.t. for 18 h, and evaporated to dryness for **3a**, **3b** and **3d**. Ac_2O was evaporated immediately after the reflux, and the dry residue (sample purified[12]) heated in air at 50 °C for 18 h for **3c**. Residues were purified by dry column vacuum chromatography[10,16] using silica gel as absorbent with gradient elution of hexane, EtOAc and MeOH as eluent

(12) **11-Hydroxy-1,4-dimethoxybenzimidazo[1,2-*b*]-isoquinolin-6 (11*H*)-one (8a):** Yellow solid; R_f = 0.63 (EtOAc–MeOH, 9:1); mp 197–200 °C (dec.); IR (neat): 2927, 1676 (C=O), 1601, 1525, 1502, 1431, 1340, 1282, 1257, 1226, 1178, 1158, 1108, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.0 Hz, 1 H), 7.82–7.75 (m, 2 H, 8,9-H), 7.63–7.60 (m, 1 H), 7.09 (s, 1 H, 11-H), 6.81 (d, *J* = 8.6 Hz, 1 H, 2,3-H), 6.62 (d, *J* = 8.6 Hz, 1 H, 2,3-H), 5.44 (br. s, 1 H, OH, disappears with D_2O), 4.11 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (C=O), 148.3, 141.8, 140.0, 138.0, 136.3 (all C), 134.4 (8,9-CH), 130.3 (C), 130.0 (CH), 128.7 (8,9-CH), 127.5 (CH), 125.1 (C), 106.6 (2,3-CH), 103.8 (2,3-CH), 76.8 (11-CH), 56.7 (CH_3), 56.3 (CH_3); HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_2O_4$: 311.1032; found: 311.1018 $[M + H]^+$.
1,4-Dimethoxy-6-oxo-6,11-dihydrobenzimidazo[1,2-*b*]isoquinolin-11-yl acetate (8b): Yellow solid; R_f = 0.56 (EtOAc); mp 171–174 °C (dec.); IR (neat): 2922, 2847, 1746 (C=O), 1679 (C=O), 1599, 1527, 1506, 1455, 1418, 1367, 1354, 1290, 1263, 1204, 1180, 1108, 1079, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, 11-H), 8.36 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.93 (d, *J* = 7.7 Hz, 1 H), 7.74–7.71 (m, 1 H, 8,9-H), 7.66–7.63 (m, 1 H, 8,9-H), 6.76 (d, *J* = 8.6 Hz, 1 H, 2,3-H), 6.65 (d, *J* = 8.6 Hz, 1 H, 2,3-H), 4.01 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 2.01 (s, 3 H, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (C=O), 169.9 (C=O), 147.8, 143.2, 141.6, 136.6, 136.1 (all C), 134.7 (8,9-CH), 130.8 (C), 130.6 (8,9-CH), 128.9 (CH), 127.8 (CH), 124.9 (C), 106.9 (2,3-CH), 104.4 (2,3-CH), 76.0 (11-CH), 56.4 (CH_3), 55.9 (CH_3), 21.2 ($COOCH_3$); HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_5$: 353.1137; found: 353.1124 $[M + H]^+$.

(13) **Benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (9)**: CAN (0.296 g, 0.54 mmol) in H_2O (5 mL) was added to **3c** (83 mg, 0.27 mmol) in MeCN (20 mL) at –5 °C. After 5 min, H_2O (20 mL) was added and the product was extracted with CH_2Cl_2 (30 mL). The organic extract was evaporated to dryness and the residue was recrystallized from $CHCl_3$. Yield: 60 mg (79%); brown solid; mp 203–205 °C (dec.); IR (neat): 1752 (C=O), 1684 (C=O), 1671 (C=O), 1583, 1515, 1494, 1396, 1358, 1287, 1259, 1239, 1189, 1062 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.32–8.30 (m, 1 H), 8.22–8.20 (m, 1 H), 8.01–7.99 (m, 2 H, 8,9-H), 6.98 [d (AB-q), *J* = 10.3 Hz, 1 H, 2,3-H], 6.93 [d (AB-q), *J* = 10.3 Hz, 1 H, 2,3-H]; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.3, 175.6, 173.7, 157.2 (all C=O), 146.6 (C), 143.4 (C), 139.1 (2,3-CH), 136.0 (8,9-CH), 135.9 (8,9-CH), 135.8 (2,3-CH), 132.8, 131.0, 130.3 (all C), 130.1 (CH), 127.4 (CH); HRMS (ESI): *m/z* calcd for $C_{15}H_7N_2O_4$: 279.0406; found: 279.0400 $[M + H]^+$.

(14) CCDC 805313 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data _request/cif, or by emailing data_request@ccdc.cam.ac.uk or by contacting The

Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033

(15) **Methyl 3-[(4,7-Dioxo-4,7-dihydro-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (11)**: Synthesis as described previously[13] with the residue recrystallized using EtOAc and hexane. Yield: 72 mg (86%); brown solid; mp 109–111 °C; IR (neat): 3408, 1671 (C=O), 1623 (C=O), 1436, 1290, 1062, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 8.83 (d, *J* = 3.6 Hz, 1 H, Pyr-6-H), 8.22 (d, *J* = 7.5 Hz, 1 H, Pyr-4-H), 7.86–7.83 (m, 1 H, Pyr-5-H), 6.78 (s, 2 H, BnIm-5,6-H), 3.75 (s, 3 H, CH_3), NH not observed; ^{13}C NMR (100 MHz, CD_3OD): δ = 184.1, 179.5 (×2), 165.3 (all C=O), 150.6 (Pyr-6-CH), 148.2 (C), 146.4 (C), 138.3 (Pyr-4-CH), 137.3 (2 × C), 137.0 (BnIm-5,6-CH), 135.4 (C), 127.2 (Pyr-5-CH), 52.5 (CH_3); HRMS (ESI): *m/z* calcd for $C_{15}H_{10}N_3O_5$: 312.0620; found: 312.0630 $[M + H]^+$.

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