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Parallel solution-phase synthesis of substituted 2-(1,2,4-triazol-3-yl)benzimidazoles

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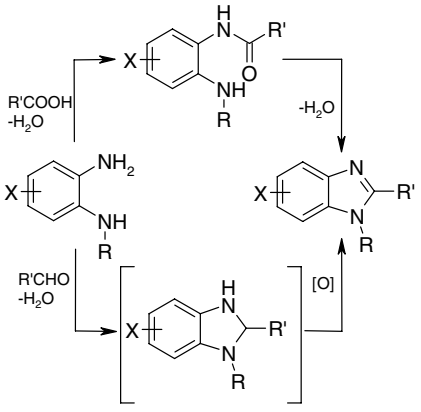
Abstract—A solution-phase synthesis for the preparation of substituted 2-(1,2,4-triazol-3-yl)benzimidazoles from triazole aldehydes and *ortho*-phenylenediamines has been developed for the purpose of producing diverse lead generation libraries. Crude products were obtained and further purified by mass-guided preparative HPLC.

The pharmaceutical industry has come to rely greatly on parallel solution-phase synthesis as a means of production for lead generation libraries of small molecules. Chemists working in this area are looking for synthetic sequences that facilitate the expedient production of large numbers of pure compounds with a high degree of structural diversity and drug-like features. Several biologically active therapeutics contain a five-membered heterocyclic ring in their chemical structures. The 1,2,4-triazole moiety is present in certain antiasthmatic, antiviral (ribavirin), antifungal (fluconazole), antibacterial, and hypnotic (triazolam) drugs.[1] Owing to its broad spectrum of biological activity, the 1,2,4-triazole ring system represents an attractive target for the elaboration of solution-phase synthesis methodology and the production of combinatorial libraries.

Only a few examples of triazole derivatives containing benzimidazole substituents are known.[2] Such compounds are of interest as targets for kinase-oriented libraries.[3] While many strategies are available for benzimidazole synthesis, the most popular approaches involve both condensation–dehydration reactions of 1,2-phenylenediamines with carboxylic acids (or their equivalents) and condensation with aldehydes under oxidative conditions (Scheme 1). Carboxylic acids or their equivalents (nitriles, amidates, and orthoesters) are usually reacted under strongly acidic or harsh dehydrating conditions that often require high temperatures or the use of reagents such as phosphorus anhydrides. The reaction can also be performed stepwise via intermediate amides. In the case of aldehydes, the reaction proceeds through a benzimidazoline, and this requires an oxidative step for conversion to the corresponding benzimidazole as shown in Scheme 1.[4]



Scheme 1. Usual methods for the preparation of benzimidazoles.

Since 1,2,4-triazole-3-carboxylic acids, especially 4-substituted examples, are not readily available, an approach via aldehydes seems to be more profitable. We synthesized a series of novel derivatives of benzimidazole using the 1,2,4-triazole-3-carbaldehydes previously

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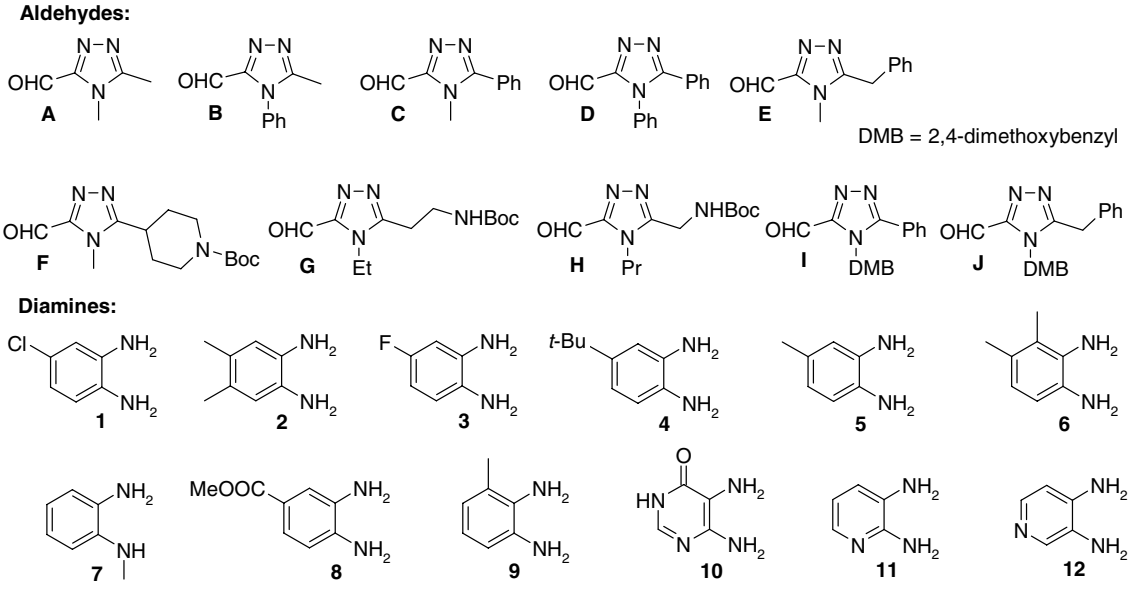
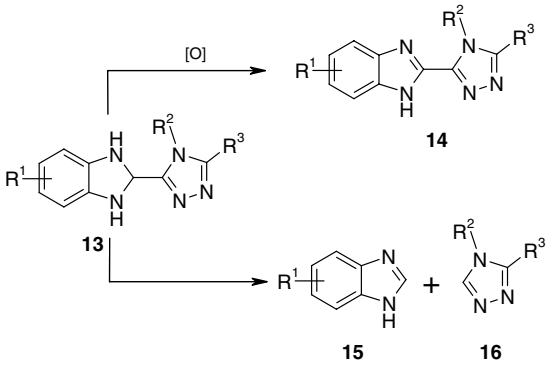


Figure 1. Sets of aldehydes and diamines for library synthesis.

described by us (Fig. 1)[5] and commercially available aryl and heteroaryl 1,2-diamines (Fig. 1). One of the mildest methods for the oxidation of the intermediate bicyclic imidazoline is the oxidation with the aerial oxygen, hence this was the method we tried first.[6]

We found that the conversion of the triazole-substituted benzimidazolines **13** into the target products **14** was accompanied by a side reaction that resulted in 2-unsubstituted benzimidazole **15** and triazole **16** (Scheme 2). This cleavage of the linking C–C bond occurred typically with 1,2-phenylenediamines possessing electron-withdrawing substituents. Thus, we found only trace amounts of the target products bearing nitro and cyano groups, and, therefore, they were excluded from the set. The same was observed for heterocyclic diamines **10**–**12** (Fig. 1). Products **14** (Scheme 2) were obtained from 1,2-phenylenediamines **1**, **3**, and **8** (Fig. 1) in much lower yields and we often failed to obtain them in an acceptably pure condition.

An another mild oxidant often used is elemental sulfur. However, its attempted use in DMF caused even more elimination of the triazole moiety. In contrast, this protocol enabled moderate yields of products obtained from heterocyclic amines **10**–**12** (Fig. 1)[7] that did not form at all via oxidation with air.



Scheme 2. Dehydrogenation or cleavage of triazole-containing benzimidazolines.

In order to increase diversity, aldehydes containing protected functional groups were employed. The results presented here relate to deprotected products **14** (Scheme 2). Note that in the case of compounds with the Boc protecting group (aldehydes **F**, **G**, and **H**) this was after HPLC purification.[8] For the compounds with the triazole ring protected by the 2,4-dimethoxybenzyl group (aldehydes **I** and **J**) we observed partial deprotection

Table 1. Yields and purities of the final products

Final products	Weight (mg)	LCMS MH+	Amount (μmol)	Purity[a] (%)	Yield[b] (%)
A5	17	228	76	99	37
A8	20	272	73	93	34
B2[11]	22	304	72	100	36
B3	23	294	78	100	39
F5	14	297	46	100	23
B8	24	334	72	94	34
I2	38	290	132	100	66
J2	23	304	76	100	38
J3	20	294	69	100	34
J4	24	332	72	97	35
J5	19	290	66	100	33
J9[11]	20	290	70	100	35
A11	20	215	94	100	47
B11[11]	30	277	107	100	54
C11	20	277	74	100	37
E11	23	291	80	98	39
E12[11]	43	291	147	96	71
G11	20	258	79	100	40
G12	30	258	115	94	54
H11	23	258	88	100	44

[a] % Purity based on HPLC analysis.
[b] % Yield calculated on the basis of the following formula: (amount/200 μmol) × purity %.

in the course of the reaction. Deprotection was carried out on the crude reaction mixtures[9] followed by HPLC purification.

The solution-phase syntheses were carried out on a 200 μmol scale in a 48-well array of glass vials and 101 final products were prepared. All the products were purified by mass-guided preparative HPLC and analyzed by HPLC (UV detection, 210 nm, 254 nm, ELSD, MSD)[10] and by ^{1}H NMR.[11] Table 1 shows the analytical results based on a theoretical yield of 200 μmol.

In conclusion, the efficiency of this synthetic methodology and wide availability of 1,2-phenylenediamines make this procedure ideally suited for the synthesis of a focused libraries.

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6. A 48-well array of 6 mL glass vials was charged with 400 μL of solutions of the corresponding aldehydes (0.2 mmol) and 400 μL of 1,2-phenylenediamines (0.2 mmol) in ethanol. The rack of tubes was covered with a Teflon/Silicone cap mat-lined plate. The reaction mixtures were vigorously stirred at 85 °C for 12 h. Then the cover was opened, and the solvent was evaporated under stirring at 85 °C. Ethanol (500 μL) was added, and the mixtures were evaporated again in the air under stirring and heating. This procedure was repeated 2–3 times. The oxidation process was monitored by HPLC. Crude products were purified by mass-guided preparative HPLC.
7. A 48-well array of 6 mL glass vials was charged with 400 μL of solutions of the corresponding aldehydes (0.2 mmol) and 400 μL of 1,2-phenylenediamines (0.2 mmol) in DMF. Sulfur powder (1 equiv) was then added. The rack of tubes was covered with a Teflon/Silicone cap mat-lined plate (not hermetically sealed because H_2S was evolved). The reaction mixtures were kept at 130 °C for 5 h, then cooled, and filtered to remove sulfur and washed with DMF (3×400 μL). The solvent was evaporated to dryness in a Savant evaporator at 60 °C for 6 h. Crude products were purified by mass-guided preparative HPLC.
8. A 4 M solution of HCl in dioxane (1 mL) was added to each vial. The reaction mixtures were stirred for 3 h. The solvent was evaporated to dryness in a Savant evaporator at 60 °C for 6 h.
9. The products were dissolved in dichloromethane (500 μL). The solutions were cooled to 0 °C in an ice bath. A mixture of TFA (1 mL), anisole (0.2 mL), and dichloromethane (2 mL) for each reaction was prepared. This mixture was added dropwise to the solutions of the products under cooling and stirring. The cooling bath was removed, and stirring was continued for 3 h. The solvent was evaporated to dryness in the air.
10. For sample purification, a 1100 LCMSD purification platform (Agilent Technologies, USA) consisting of two preparative pumps, an autosampler, a variable wavelength detector, a fraction collector, and a mass-spectrometric detector was used. A Kromasil 7 μm C18 150×30 mm column (Akzo Nobel, Sweden) was employed. Gradient separation was used from 10% acetonitrile, 90% water, 0.1% TFA to 0.1% TFA in acetonitrile. For quality control a 1100 LCMSD (Agilent Technologies, USA) was used. A Hi-Q 5 μm C18 50×4.6 mm column (Peeke Scientific, USA) was used. The gradient separation was from 2.5% acetonitrile, 97.5% water, 0.1% TFA to 0.1% TFA in acetonitrile.
11. Data for selected products. Compound **B2**: (DMSO-d_6, 400 MHz) δ 2.26 (br s, 9H), 7.23 (s, 2H), 7.45–7.49 (m, 2H), 7.53–7.57 (m, 3H). Anal. Calcd for $C_{18}H_{17}N_5$ (303.37): C, 71.27; H, 5.65; N, 23.09. Found: C, 71.31; H, 5.66; N, 22.94. Compound **B11**: (DMSO-d_6, 400 MHz) δ 2.28 (s, 3H), 7.26 (dd, 1H, $J = 7.7$ Hz, $J = 4.6$ Hz), 7.50–7.55 (m, 2H), 7.55–7.60 (m, 3H), 7.92 (dd, 1H, $J = 7.7$ Hz, $J = 1.5$ Hz), 8.35 (dd, 1H, $J = 4.6$ Hz, $J = 1.5$ Hz). Anal. Calcd for $C_{15}H_{12}N_6$ (276.30): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.19; H, 4.39; N, 30.31. Compound **J9**: (DMSO-d_6, 400 MHz) δ 2.60 (s, 3H), 4.24 (s, 2H), 7.17 (br d, 1H, $J = 7.8$ Hz), 7.24–7.31 (m, 2H), 7.33–7.38 (m, 4H), 7.46 (d, 1H, $J = 7.8$ Hz). Anal. Calcd for $C_{17}H_{15}N_5 \cdot 0.92CF_3COOH$ (394.24): C, 57.40; H, 4.07; N, 17.76. Found: C, 57.43; H, 4.67; N, 17.32. Compound **E12**: (DMSO-d_6, 400 MHz) δ 4.04 (s, 3H), 4.36 (s, 2H), 7.25–7.32 (m, 3H), 7.33–7.39 (m, 2H), 7.99 (d, 1H, $J = 6.4$ Hz), 8.58 (d, 1H, $J = 6.4$ Hz), 9.43 (s, 1H). Anal. Calcd for $C_{16}H_{14}N_6 \cdot 0.95CF_3COOH$ (398.65): C, 53.93; H, 3.78; N, 21.08. Found: C, 54.28; H, 3.84; N, 21.19.