Dibenzo[bd]pyrazolo[1,5-d][1,4]oxazepines: a facile construction of a rare heterocyclic system via tandem aromatic nucleophilic substitution - Smiles rearrangement - denitrocyclization

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Abstract: Condensation of 2-(1H-pyrazol-5-yl)phenols with o-chloronitrobenzenes under basic conditions in DMF results in a tandem, atom-economical aromatic nucleophilic substitution – Smiles rearrangement – denitrocyclization process to provide pyrazolo-fused dibenzo[bd][1,4]oxazepines as a single regioisomer.

Key words: tetracyclic scaffolds, privileged structures, atom-economical syntheses, dibenzo[bd][1,4]oxazepines, Smiles rearrangement, nucleophilic aromatic substitution, denitrocyclization, regiospecific reaction.

The range of biological activities displayed by the compounds containing dibenzo[bd][1,4]oxazepine scaffold is strikingly vast. From the early applications of such compounds as psychotropic drugs (e.g., Loxapine, 1) and, even more prominently, as prostaglandin receptors antagonists (e.g., Searle’s SC-19220, 2), the utility of dibenzo[bd][1,4]oxazepines has recently extended to the design of potent progesterone receptor antagonists (3), p38 MAP kinase inhibitors (4), TRPA1 ion channel modulators (5) and histone deacetylase inhibitors (6) (Figure 1). This provides ample evidence for the privileged character of this scaffold (as defined by Evans’) and makes the development of novel synthetic methodologies toward this and related heterocyclic systems particularly worthwhile.

Figure 1. Examples of pharmacologically active dibenzo[bd][1,4]oxazepines.

Scheme 1. Strategies for construction of the dibenzo[bd][1,4]oxazepine scaffold: (a) described earlier 9 and (b) investigated in present work.
Of special value are tandem synthetic strategies that are atom-economical, generally more efficient and less time-consuming than linear multistep ones. Earlier, we reported a practically simple and streamlined entry into dibenzo[b,f][1,4]oxazepin-11(10H)-ones and their 9-aza analogs via condensation of o-chloronitro derivatives of benzene and pyridine, respectively, with secondary salicylamides under basic conditions. The reaction proceeded, as anticipated, via a denitrocyclization step but was accompanied by unexpected (though not unprecedented) Smiles rearrangement of the initial diaryl ether adduct. Encouraged by this finding, we became curious if NH-acidic azoles such as pyrazole could be effective participants in a similar tandem process in lieu of the secondary amide functionality. This would lead to the formation of a rare pyrazole-including framework Scheme 1. Such tetracyclic scaffolds are of much interest considering that fusion of five-membered cycles onto a dibenzo[b,f] pyrazolo[1,5-d][1,4]oxazepine core has been shown to attenuate the pharmacological properties of the resulting compounds. Moreover, dibenzo[b,f]pyrazolo[1,5-d][1,4]oxazepines have recently found application in the design of organic light emitting devices (OLEDs).

Herein, we would like to report on a successful realization of a new synthetic strategy toward dibenzo[b,f]pyrazolo[1,5-d][1,4]oxazepines.

The starting 2-(1H-pyrrozol-5-yl)phenols 14a-e were prepared via a Claisen condensation of o-hydroxycetophenones followed by treatment of the isolated sodium phenolates with hydrazine hydrate (Scheme 2). Both steps involved only filtration as the means of solid product isolation and provided good to excellent yields of the desired material (Table 1).

### Scheme 2. Preparation of 2-(1H-pyrrozol-5-yl)phenols 14a-e.

![Scheme 2](image-url)

Table 1. 2-(1H-Pyrrozol-5-yl)phenols 14a-e and their precursors 17a-e synthesized in this work.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>Yield of 17 (%)</th>
<th>Yield of 14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14(17)a</td>
<td>H</td>
<td>H</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>14(17)b</td>
<td>H</td>
<td>Me</td>
<td>60</td>
<td>76</td>
</tr>
<tr>
<td>14(17)c</td>
<td>H</td>
<td>Et</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td>14(17)d</td>
<td>Cl</td>
<td>Me</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>14(17)e</td>
<td>Me</td>
<td>Me</td>
<td>72</td>
<td>63</td>
</tr>
</tbody>
</table>

To our delight, compounds 14a-e underwent a facile condensation with a set of o-chloronitrobenzenes, on heating with 3 equiv. of anhydrous potassium carbonate in DMF. Moreover, H NMR analyses of the crude reaction mixtures confirmed the disappearance of the characteristic broad singlets corresponding to both the pyrazole moiety (N-H 13.55…12.70 ppm) and the phenol functionality (O-H 11.40…10.03 ppm), clearly indicating that the former participated in the reaction. Additionally, the H NMR signals corresponding to the aromatic portions of 14 and 18 exhibited pronounced (~0.3 ppm) downfield and upfield shifts, respectively. This, according to our previous denitrocyclization experience, strongly attested to the formation of the hitherto non-described tetracyclic compounds 19a-o.

### Scheme 3. Preparation of dibenzo[b,f]pyrazolo[1,5-d][1,4]oxazepines 19a-o.

![Scheme 3](image-url)

Table 2. Dibenzo[b,f]pyrazolo[1,5-d][1,4]oxazepines 19a-o synthesized in this work.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19a</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>66</td>
</tr>
<tr>
<td>19b</td>
<td>H</td>
<td>H</td>
<td>CN</td>
<td>79</td>
</tr>
<tr>
<td>19c</td>
<td>H</td>
<td>H</td>
<td>NO2</td>
<td>81</td>
</tr>
<tr>
<td>19d</td>
<td>H</td>
<td>Me</td>
<td>COOMe</td>
<td>77</td>
</tr>
<tr>
<td>19e</td>
<td>H</td>
<td>Me</td>
<td>CN</td>
<td>81</td>
</tr>
<tr>
<td>19f</td>
<td>H</td>
<td>Me</td>
<td>NO2</td>
<td>68</td>
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<tr>
<td>19g</td>
<td>H</td>
<td>Et</td>
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<td>60</td>
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<tr>
<td>19h</td>
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<td>73</td>
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<td>85</td>
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<tr>
<td>19j</td>
<td>Cl</td>
<td>Me</td>
<td>COOMe</td>
<td>74</td>
</tr>
<tr>
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<td>Cl</td>
<td>Me</td>
<td>CN</td>
<td>83</td>
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<td>19l</td>
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<td>NO2</td>
<td>85</td>
</tr>
<tr>
<td>19m</td>
<td>Me</td>
<td>Me</td>
<td>COOMe</td>
<td>76</td>
</tr>
<tr>
<td>19n</td>
<td>Me</td>
<td>Me</td>
<td>CN</td>
<td>69</td>
</tr>
<tr>
<td>19o</td>
<td>Me</td>
<td>Me</td>
<td>NO2</td>
<td>80</td>
</tr>
</tbody>
</table>

The isolated yield of compounds 19a-o were good to excellent (Table 2) and their analytical data (H and C NMR as well elemental analyses) were consistent with the anticipated dibenzo[b,f]pyrazolo[1,5-d][1,4]oxazepine structure. However, establishing the regiochemical identity of the products obtained presented a significant challenge, although it was evident from the NMR data that compounds 19a-o belonged to the same isomeric series. Presumably, the regiochemistry of 19 would be determined (Scheme 4) by the ability of the pyrazole moiety to participate in the initial chlorine displacement event (path a) or in the
subsequent Smiles rearrangement (path b) of the initially formed diphenyl ether adduct 20. In both cases regioisomer A would be formed in contrast to regioisomer B that might result from two sequential nucleophilic displacements (of the chlorine atom and the nitro group), not accompanied by the Smiles rearrangement (path c), a possibility that also should be considered.

Scheme 4. Possible reaction pathways determining the regiochemistry of dibenzo[h,j]pyrazolo[1,5-d][1,4]oxazepines 19a-o.

Intermolecular displacement of the chlorine atom in 18 by the pyrazole moiety in 14 (path a) can be easily ruled out based on the results of a model experiment. Under the same reaction conditions, 3-methyl-5-phenyl-1H-pyrazole (21) failed to react with 4-chloro-3-nitrobenzonitrile (22), even on prolonged (3 days) heating at 110 °C (Scheme 5). Additionally, the absence in the reaction mixture of pyrazole N-arylation products regioisomeric to intermediate 20' (which cannot be expected to participate in subsequent cyclization events due to steric reasons) also speak against the reaction’s proceeding via path a.

Scheme 5. Attempted reaction of a model pyrazole 21 with 3-chloro-4-nitrobenzonitrile (22).

Unfortunately, correlational NMR spectroscopy (NOESY, HSQC, HMBC) provided insufficient information for an unequivocal regiochemistry assignment of products 19a-o and thus for distinguishing between the reaction paths b and c. To our relief, we were able to obtain a single-crystal X-ray structure of a representative compound, 19h (Figure 2). It clearly showed the compound’s belonging to the isomeric series A and thus confirmed that the compounds 19 formed as a result of tandem aromatic nucleophilic substitution – Smiles rearrangement – denitrocyclization.

In summary, we have developed a streamlined synthetic methodology toward hitherto not described dibenzo[h,j]pyrazolo[1,4]oxazepines from readily available precursors. The compounds were obtained in high yields as a single regioisomer as a result of three chemical events occurring in tandem. This represents a remarkable example of atom economy and efficiency in constructing polycyclic heterocycles. Similar strategies involving other potentially nucleophilic azoles are being investigated in our laboratories and will be reported in due course.

Figure 2. Single-crystal X-ray structure of compound 19h.
using an appropriate mixture of ethyl acetate and hexane. Compounds were visualized with short-wavelength UV light. 1H NMR and 13C NMR spectra were recorded on Bruker MSL-300 spectrometers in DMSO-d6, using TMS as an internal standard. Elemental analyses were obtained at Research Institute for Chemical Crop Protection (Moscow, Russia) using Carlo Erba Strumentazione 1106 analyzer. The IR spectra were recorded using Specord M-80 spectrophotometer on compound samples prepared as KBr tablets. All and reagents were obtained from commercial sources and used without purification. DMF was dried according to the standard procedure 13 and potassium carbonate was dried at 200 °C for 5 hours prior to use.

### 4-Chloro-2-(3-methyl-1H-pyrazol-5-yl)phenol (14d)

Typical Procedure for the Synthesis of Compounds

Sodium metal (6.44 g, 0.280 mol) was carefully added to a solution of 5'-chloro-2'-hydroxyacetophenone (11.9 g, 0.070 mol) in ethyl propanoate (100 mL) over 1 hour. The resulting mixture (total volume – 1 L). The resulting precipitate cooled down to rt and poured over crushed ice – water. The resulting mixture was heated at reflux for 2 h, overnight to provide 10.9 g (67%) of 1-(5-chloro-2'-hydroxyacetophenone (11.9 g, 0.070 mol).

A solution of 5'-chloro-2'-hydroxyacetophenone (11.9 g, 0.070 mol) in ethyl propanoate (100 mL) was added to a solution of hydrazine hydrate (65% solution in water, 5 mL) and glacial acetic acid (0.021 mol) were added to a solution of this compound (3.65 g, 0.016 mol) in ethanol (30 mL). The resulting mixture was heated at reflux for 5 h, cooled down to rt and the volatiles were removed in vacuo. The resulting precipitate was filtered off, washed with cold isopropyl alcohol (50 mL), air dried and further dried in vacuum at 60 °C overnight to provide 10.9 g (67%) of 1-(5-chloro-2'-hydroxyacetophenone (11.9 g, 0.070 mol).

1H NMR (DMSO-d6, 300 K, ppm): δ 12.80…13.09 (br s, 1H, pyrazole NH), 10.97…11.21 (br s, 1H, ArOH), 7.63 (d, J = 7.9 Hz, 1H, Ar), 7.15 (t, J = 7.9 Hz, 1H, Ar), 6.82…6.94 (m, 2H, Ar), 6.59 (s, 1H, Pyrazole CH), 2.30 (s, 3H, CH3).

1C NMR (DMSO-d6, 300 K, ppm): δ 155.3, 128.6, 126.8, 119.2, 119.1, 117.2, 116.4, 101.0.

Anal. Calcd for C10H9ClN2O: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.31; H, 4.03; N, 13.49.

### Off-white solid; mp 50-52 °C.

White solid; mp 50-52 °C.

1H NMR (DMSO-d6, 300 K, ppm): δ 13.04…13.55 (br s, 1H, pyrazole NH), 10.86…11.18 (br s, 1H, ArOH), 7.60 (d, J = 7.5 Hz, 1H, Ar), 7.12 (t, J = 7.0 Hz, 1H, Ar), 6.84 (m, 2H, Ar), 6.53 (s, 1H, Pyrazole CH), 2.70 (m, 2H, CH2CH3), 1.28 (t, J = 7.5 Hz, CH2CH3).

1C NMR (DMSO-d6, 300 K, ppm): δ 155.3, 128.6, 126.5, 119.2, 119.1, 117.3, 116.4, 99.9, 18.5, 13.4.

Anal. Calcd for C10H12N2O: C, 70.01; H, 6.44; N, 14.95.

White solid; mp 50-52 °C.

1H NMR (DMSO-d6, 300 K, ppm): δ 13.04…13.55 (br s, 1H, pyrazole NH), 10.86…11.18 (br s, 1H, ArOH), 7.60 (d, J = 7.5 Hz, 1H, Ar), 7.12 (t, J = 7.0 Hz, 1H, Ar), 6.84 (m, 2H, Ar), 6.53 (s, 1H, Pyrazole CH), 2.70 (m, 2H, CH2CH3), 1.28 (t, J = 7.5 Hz, CH2CH3).

1C NMR (DMSO-d6, 300 K, ppm): δ 155.3, 128.6, 126.5, 119.2, 119.1, 117.3, 116.4, 99.9, 18.5, 13.4.

Anal. Calcd for C10H12N2O: C, 70.01; H, 6.44; N, 14.95.

White solid; mp 128-131 °C.

1H NMR (DMSO-d6, 300 K, ppm): δ 13.00…13.49 (br s, 1H, pyrazole NH), 10.73…11.08 (br s, 1H, ArOH), 7.86 (s, 1H, Pyrazole CH), 7.72 (d, J = 7.9 Hz, 1H, Ar), 7.17 (t, J = 7.5 Hz, 1H, Ar), 6.79…6.95 (m, 3H, Ar + Pyrazole).

1C NMR (DMSO-d6, 300 K, ppm): δ 155.3, 139.1, 128.6, 126.8, 126.7, 119.2, 119.1, 117.2, 116.4, 101.0.

Anal. Calcd for C10H9ClN2O: C, 67.49; H, 5.03; N, 17.49.

White solid; mp 128-131 °C.
Methyl 2-ethylidibenzoi[f]pyrazolo[1,5-d][1,4]oxazepine-10-carboxylate (19a).

Yield 0.78 g (66%).

White solid; mp 94-96 °C.

IR (KBr): 1682, 1619, 1223, 1200 cm⁻¹.

1H NMR (DMSO-d₆, 300 K, ppm): δ 8.01 (s, 1H, Ar), 7.83...7.96 (m, 2H, Ar), 7.69 (d, J = 7.9 Hz, 1H, Ar), 7.57 (d, J = 8.2 Hz, 1H, Ar), 7.49 (t, J = 7.2 Hz, 1H, Ar), 7.33 (t, J = 7.2 Hz, 1H, Ar), 6.87 (s, 1H, pyrazole CH), 3.88 (s, 3H, COOCH₃), 2.71 (m, 2H, CH₂CH₃), 1.29 (t, J = 7.9 Hz, 3H, CH₂CH₃).


Found: C, 70.98; H, 6.24; N, 14.91.

5-Nitrodibenzo[i]pyrazolo[1,5-d][1,4]oxazepine (19b).

Yield 0.67 g (81%).

White solid; mp 173-175 °C (EtOH).

IR (KBr): 1744, 1623, 1219, 1201 cm⁻¹.

1H NMR (DMSO-d₆, 300 K, ppm): δ 8.01 (s, 1H, Ar), 7.83...7.96 (m, 2H, Ar), 7.69 (d, J = 7.9 Hz, 1H, Ar), 7.57 (d, J = 8.2 Hz, 1H, Ar), 7.49 (t, J = 7.2 Hz, 1H, Ar), 7.33 (t, J = 7.2 Hz, 1H, Ar), 6.87 (s, 1H, pyrazole CH), 3.88 (s, 3H, COOCH₃), 2.71 (m, 2H, CH₂CH₃), 1.29 (t, J = 7.9 Hz, 3H, CH₂CH₃).


Found: C, 70.98; H, 6.24; N, 14.91.

Methyl 2-ethylidibenzoi[f]pyrazolo[1,5-d][1,4]oxazepine-10-carboxylate (19a).

Yield 0.78 g (66%).

White solid; mp 94-96 °C (EtOH).

IR (KBr): 1682, 1619, 1223, 1200 cm⁻¹.

1H NMR (DMSO-d₆, 300 K, ppm): δ 8.01 (s, 1H, Ar), 7.83...7.96 (m, 2H, Ar + pyrazole), 7.69 (d, J = 7.9 Hz, 1H, Ar), 7.57 (d, J = 8.2 Hz, 1H, Ar), 7.49 (t, J = 7.2 Hz, 1H, Ar), 7.33 (t, J = 7.2 Hz, 1H, Ar), 6.87 (s, 1H, pyrazole CH), 3.88 (s, 3H, COOCH₃), 2.71 (m, 2H, CH₂CH₃), 1.29 (t, J = 7.9 Hz, 3H, CH₂CH₃).


Found: C, 70.98; H, 6.24; N, 14.91.
2-Methyl-10-nitrodibenzo[bf]pyrazolo[1,5-d][1,4]oxazepine (19f).

Yield 0.88 g (68 %).

Dark-yellow solid; mp 237-239 °C (EtOH/DMF).

IR (KBr): 1680, 1617, 1352 cm⁻¹.

1H NMR (DMSO-d₆, 300 K, ppm): δ 8.42 (s, 1H, Ar), 7.97 (d, J = 9.2 Hz, 1H, Ar), 7.56 (t, J = 7.9 Hz, 1H, Ar), 2.37 (s, 3H, CH₃).


13C NMR (DMSO-d₆, 300 K, ppm): 156.5, 155.1, 152.2, 149.3, 141.3, 136.7, 135.9, 131.9, 130.5, 129.7, 129.3, 128.8, 127.5, 126.3, 124.1, 120.9, 117.7, 107.8, 21.1, 13.2.


**Methyl 5-chloro-2-methylidibenzof[b furyl]pyrazolo[1,5-d][1,4]oxazepine-10-carboxylate (19j).**

Yield 0.73 g (74 %).

Grey solid; mp 192-195 °C (DMF).

IR (KBr): 1745, 1620, 1224, 1205 cm⁻¹.
2,5-Dimethylidibenzo[bf]pyrazolo[1,5-d][1,4]oxazepine-10-carbonitrile (19a).

Yield 0.63 g (69%).

Light-yellow solid; mp 182-185 °C (EtOH/DMF).

IR (KBr): 2241, 1608 cm⁻¹.

1H NMR (DMSO-d₆, 300 K, ppm): δ 8.08 (s, 1H, Ar), 7.90 (d, J = 8.5 Hz, 1H, Ar), 7.79 (d, J = 7.9 Hz, 1H, Ar), 7.50 (1H, Ar), 7.27…7.42 (m, 2H, Ar), 6.83 (s, 1H, pyrazole CH), 2.35 (s, 3H, ArCH₃), 2.32 (s, 3H, pyrazole CH₃).

13C NMR (DMSO-d₆, 300 K, ppm): δ 153.2, 151.7, 149.2, 141.3, 136.7, 135.9, 132.0, 129.3, 126.3, 124.1, 121.0, 120.9, 117.7, 109.9, 107.6, 20.3, 13.5.


Found: C, 75.11; H, 4.56; N, 14.68.

2,5-Dimethyl-10-nitrodibenzo[bf]pyrazolo[1,5-d][1,4]oxazepine (19o).

Yield 1.38 g (80%).

Dark-grey solid; mp 207-209 °C (EtOH/DMF).

IR (KBr): 1685, 1619, 1354 cm⁻¹.

1H NMR (DMSO-d₆, 300 K, ppm): δ 8.39 (s, 1H, Ar), 8.21 (d, J = 8.9 Hz, 1H, Ar), 7.99 (d, J = 8.9 Hz, 1H, Ar), 7.47…7.56 (m, 2H, Ar), 7.33 (d, J = 8.5 Hz, 1H, Ar), 6.87 (s, 1H, pyrazole CH), 2.36 (s, 3H, ArCH₃), 2.33 (s, 3H, pyrazole CH₃).

13C NMR (DMSO-d₆, 300 K, ppm): δ 153.1, 152.1, 148.8, 145.8, 141.4, 138.1, 136.1, 132.1, 129.3, 123.7, 121.7, 121.2, 120.8, 118.0, 107.9, 20.3, 13.5.


Found: C, 66.25; H, 4.23; N, 13.71.

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References and notes

(14) Crystallographic data (excluding structure factors) for the structure 19h have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 871488. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
