

## Three-Component Synthesis of (Pyrrolo)quinazolines

Category

Synthesis of Heterocycles

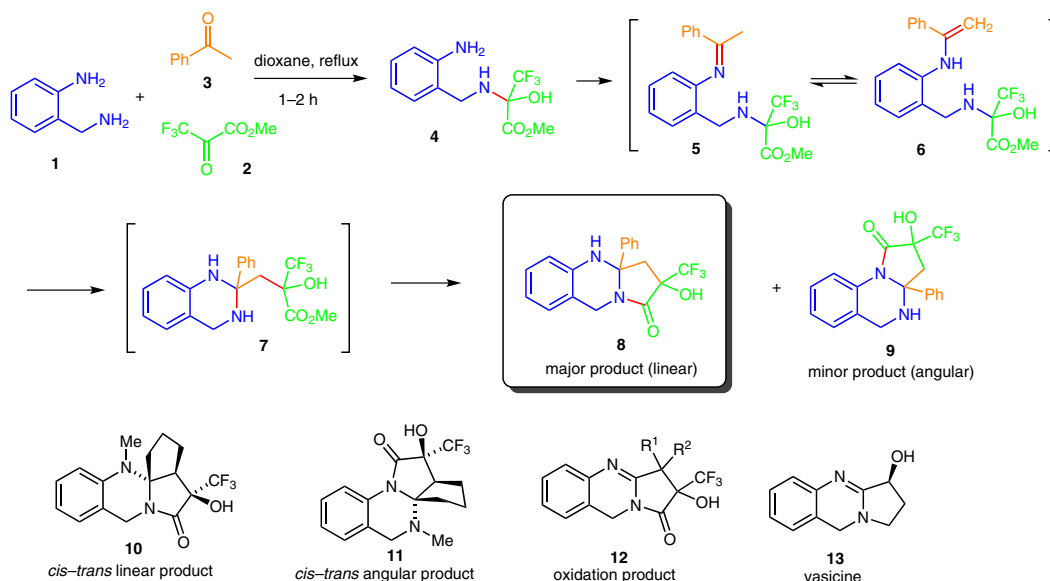
Key words

three-component reaction

pyrroloquinazolines

nucleophilic rearrangement

**SYNFACT**  
*of the month*



**Significance:** By combining three components, 2-aminobenzylamine **1**, a reactive carbonyl compound (such as trifluoropyruvate) **2**, and a ketone (or aldehyde) **3**, (pyrrolo)quinazolines are formed by a heteroannulation process which involves an interesting rearrangement from **6** to **7**. A detailed mechanistic study of the process was carried out, providing evidence that the reaction proceeds via the hemiaminal **4** and Schiff base **5**, which is in equilibrium with its enamine **6**. This step is followed by an unusual intramolecular cyclization–migration sequence. Alternative lactam ring closure occurs, forming the tricyclic products **8** or **9**. The linearly annulated (pyrrolo)quinazoline **8** (major product) conveniently possess the skeleton of alkaloids of the vasicine group (**13**). The quinazoline derivatives in general exhibit a variety of biological activities.

**Comment:** This report builds on previous work by the same authors on the synthesis of (pyrrolo)quinazolines and the reactivity of trifluoropyruvate hemiaminals (*Eur. J. Org. Chem.* **2013**, 1262; *J. Fluorine. Chem.* **2005**, 126, 745). The cyclization proceeds with high regio- and stereoselectivities for the particular carbonyl compounds and is temperature dependent. Complete selectivity of the reaction can be achieved utilizing *N*-mono-methylated aminobenzylamine as a starting material, affording exclusively the linear or angular products **10** or **11** using cyclopentanone as the starting ketone. Certain linear products can be oxidized by the excess of trifluoropyruvate, forming **12** with complete regioselectivity. The authors unambiguously established the relative configuration on the stereogenic centers utilizing a sophisticated combination of homo- and heteronuclear NOE experiments (*Magn. Res. Chem.* **2010**, 48, 375).