Auto-Oxidative Coupling of Glycine Derivatives


**Significance:** The reported auto-oxidation of \( N \)-aryl glycines 1 afforded a versatile imine intermediate, which underwent the Povarov annulation affording 3; further oxidation led to 4, while nucleophilic addition afforded 5. When 2,3-dihydrofuran was employed in the Povarov reaction, a subsequent ring opening–ring closing sequence was observed, resulting in the isolation of compound 3c. The reported Povarov reaction, in particular, is complementary to existing reactions of anilines with glyoxalates and terminal alkynes under acidic catalysis (for example, see: J. B. Bharate et al. *Org. Biomol. Chem.* 2014, 12, 6267) and avoids the selectivity issues associated with the functionalization of bishalogenated quinolines.

**Comment:** Although a more extensive demonstration of substrate scope or functional group tolerance would have been appreciated in the presented synthesis, highlights include the tolerance of \( N \)-acyl glycines, allyl esters, and halides. Oxidation side products 4 were always observed in the Povarov annulations, but were minimized when \( R^2 \) was an electron-rich substituent. The reaction rates were found to be highly dependent on solvent choice, with a 5:1 mixture of MeCN and DCE required for optimal reactivity. The reaction efficiency was also noted to depend on the use of 3–5 week old DCE or on the addition of a trace quantity of HCl, an observation that will impact the reproducibility of these results without due attention.

**Selected examples:**

- 3a 47% yield (9% 4)
- 3b 28% yield (7% 4)
- 3c 35% yield (40% 4)
- 3c 42% yield (2 = 2,3-dihydrofuran)

**Other reactions also reported:**

- 4 52% yield (occurs in the absence of a reaction partner)
- 5 (74% yield)

SYNFACTS Contributors: Victor Snieckus, Benjamin N. Rocke (Pfizer)

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.