

Passerini/Friedel-Crafts Route towards indole Derivatives.

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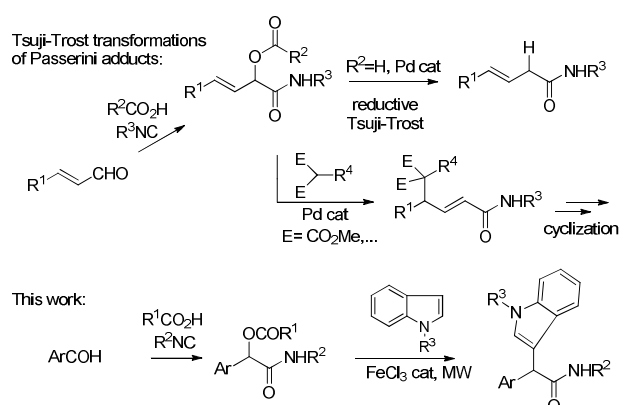
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Received: The date will be inserted once the manuscript is accepted.

Abstract: The Passerini adducts of various electron-rich aromatic aldehydes with pivalic acid were used as electrophiles towards indoles in a Friedel-Crafts type reaction. The Friedel-Crafts step was performed under microwave conditions using a catalytical amount of FeCl₃.

Key words: Passerini, Friedel-Crafts, indoles, iron chloride catalyst.

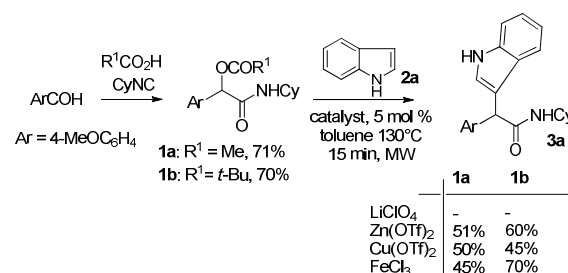
The coupling of aldehydes, isocyanides and carboxylic acids was discovered by Passerini nearly a century ago.¹ The interest for the reaction was renewed after the success of the Ugi reaction in promoting multicomponent processes for the formation of libraries of heterocycles.² The comparison with the Ugi reaction and its 4-component nature is not in favor of the Passerini coupling in terms of synthetic potential. However, considering the latter reaction, one may take advantage of the formation of a rather weak C-O bond in synthetic strategies involving subsequent substitution or elimination processes.³ We have recently exploited this strategy in various Tsuji-Trost reactions of cinnamaldehyde Passerini adducts leading to reduction or substitution of an acetoxy group by malonyl derivatives (Scheme 1),⁴ we now wish to present some further substitutions involving Passerini adducts in Friedel-Crafts type reactions with indoles (Scheme 1).



Scheme 1 Passerini couplings followed by substitution of the carboxylate group.

Electron-rich aromatic aldehydes are known to be good partners in Passerini reactions. The generation of benzylic cationic intermediates through elimination of a carboxylate group from the resulting adducts is expected to be greatly enhanced by the release of electron from the aromatic moiety. To test the

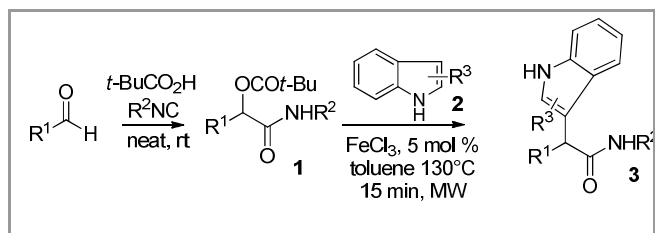
potential trapping of such cationic intermediates by indoles, the Passerini adduct **1a** was prepared in 71% isolated yield from 4-methoxybenzaldehyde, cyclohexyl isocyanide and acetic acid (Scheme 2). When **1a** was heated in toluene under microwave conditions with stoichiometric amounts of indole **2a** and in the presence of 5 mol% of Zn(OTf)₂, we were delighted to observe the formation of the expected Friedel-Craft adduct **3a**. However, the latter was only obtained in a moderate 51% isolated yield (Scheme 2). Using FeCl₃, LiClO₄ or Cu(OTf)₂ didn't improve much the reaction. The effect of the leaving group was also evaluated by replacing acetic acid by pivalic acid in the Passerini step. Though adduct **1b** was obtained in a comparable 70% isolated yields, the elimination step proceeds much more efficiently leading to **3a** in 70% isolated yield when using 5 mol % of FeCl₃ as catalyst (Scheme 2).



Scheme 2 Passerini couplings followed by carboxylate group elimination.

Thus, pivalic acid and FeCl₃ as catalyst were selected for this new Passerini/Friedel-Craft sequence and these conditions applied for the various Passerini adducts presented in Table 1.⁵ The need for an electron rich aromatic aldehyde was confirmed by the lack of reactivity of the 4-chlorobenzaldehyde Passerini adduct **1e** under these conditions (Table 1, entry 3). In contrast, a coupling between indole **2a** and cinnamaldehyde adduct **1g** was observed in moderate yield (Table 1, entry 8). This could be explained by an increased stabilization a cationic reactive intermediate through further conjugation on the aryl ring and the double bond. The sequence is not limited to cyclohexyl isocyanide as shown by the formation of indoles **3b** and **3c** using *t*-butyl and 4-methoxybenzyl isocyanides (Table 1, entries 1-2). Finally furfural could be used as well in this sequence leading to indoles **3g** and **3h** in moderate yield (Table 1, entries 6-7).

Table 1



Entry	1	Yield	3	Yield
1		75%		60%
2		80%		70%
	Ar=4-MeOC ₆ H ₄		Ar=4-MeOC ₆ H ₄	
3		75%		0%
4	1b	70%		73%
5	1b	70%		53%
6		85%		32%
7	1f	85%		45%
8		70%		40%

Though, this new two-steps preparation of indole derivatives is limited to rather electron rich aldehydes,

it gives a fast access to important medicinally relevant scaffolds with a good level of diversity.⁶ The originality of the sequence is further raised by the use of a widely available and cheap catalyst in small amounts. Related Friedel-Crafts additions of α -hydroxy amide derivatives on indoles have been usually performed with stoichiometric amounts of strong Bronsted acids.⁷

To conclude, we have proposed a new application of the Passerini reaction by disclosing Friedel-Craft type additions of Passerini adducts on the 3-position of indoles. The use of multicomponent reactions to get access to indoles derivatives has been the object of important research efforts.⁸ Among the isocyanides based MCRs, most synthetic strategies towards these scaffolds have displayed a Ugi reaction as the key step for diversity.⁹ We are working further on the extension of this Passerini-based strategy to the use of less electron-rich aldehydes as well as other families of nucleophiles.

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Acknowledgment

E. H. E. M. thanks the MESRS of Algeria and the USTO for a PhD fellowship. We thank the ENSTA ParisTech for financial support.

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Preparation of **1b**: A mixture of *p*-anisaldehyde (0.37 ml, 3.0 mmol), pivalic acid (0.31 g, 3.0 mmol), and cyclohexyl isocyanide (0.38 ml, 3.0 mmol) was stirred at room temperature for 3 days. Purification by flash chromatography with a gradient Et₂O/EP (40/60 to 80/20) gave the desired **1b** as a white solid in 70% isolated yield (729 mg, 2.1 mmol). M.P. = 142-143 °C. R_f: 0.43 (70:30 diethyl ether / petroleum ether). ¹H NMR (CDCl₃, 400 MHz): δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.03 (d, *J* = 7.8 Hz, 1H), 5.96 (s, 1H), 3.86-3.70 (m, 4H), 1.91-1.80 (m, 2H), 1.69-1.52 (m, 3H), 1.40-1.29 (m, 2H), 1.23 (s, 9H), 1.19-1.04 (m, 3H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 176.4, 167.7, 159.8, 128.6, 128.0, 114.0, 74.8, 55.2, 47.9, 38.7, 32.8, 27.0, 25.4, 24.6. HRMS: calculated for C₂₀H₂₉NO₄: 374.2097, found: 374.2103. I.R. (thin film): 3435, 3041, 3003, 2946, 2857, 1734, 1679, 1613, 1587, 1533, 1526, 1513, 1453, 1305, 1249, 1186, 1142, 1035, 941, 834 cm⁻¹.
Preparation of **3a**: To a solution of Passerini adduct **1b** (100 mg, 0.29 mmol) in toluene (1 ml, 0.33 M) were added indole 2a (34 mg, 0.29 mmol) and FeCl₃ (0.05 equiv). The resulting mixture was heated at 120°C for 15 min under microwave conditions (CEM Discover microwave, 150 W). After removal of the solvent under reduced pressure, the crude was purified by flash chromatography (gradient AcOEt/EP 40/60 to 50/50) to afford **3a** as a red oil in 83% isolated yield (83 mg, 0.229 mmol). R_f: 0.25 (40:60 ethyl acetate / petroleum ether). ¹H NMR (CDCl₃, 400 MHz): δ 8.72 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.32-7.28 (m, 2H), 7.21 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.11 (dd, *J* = 11.0, 4.0 Hz, 1H), 6.92-6.84 (m, 3H), 5.84 (d, *J* = 8.2 Hz, 1H), 5.09 (s, 1H), 3.97-3.87 (m, 1H), 3.83 (s, 1H), 1.96-1.83 (m, 2H), 1.67-1.57 (m, 3H), 1.39-1.27 (m, 2H), 1.12-0.97 (m, 3H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 171.9, 158.6, 136.7, 131.8, 129.6, 126.5, 124.1, 122.3, 119.7, 119.1, 114.8, 114.1, 111.5, 55.3, 50.5, 48.4, 33.0, 32.9, 25.4, 24.8. HRMS: calculated for C₂₃H₂₆N₂O₂: 362.1994, found: 362.1985. I.R. (thin film): 3478, 3406, 3009, 2936, 2857, 1652, 1611, 1514, 1457, 1416, 1338, 1303, 1250, 1179, 1095, 1035, 909 cm⁻¹.
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