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Authors: laurent El Kaim and Noisette Narboni

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Passerini/Tsuji-Trost strategy towards pyrrole derivatives

Noisette Narboni[a] and Laurent El Kaim,*[a]

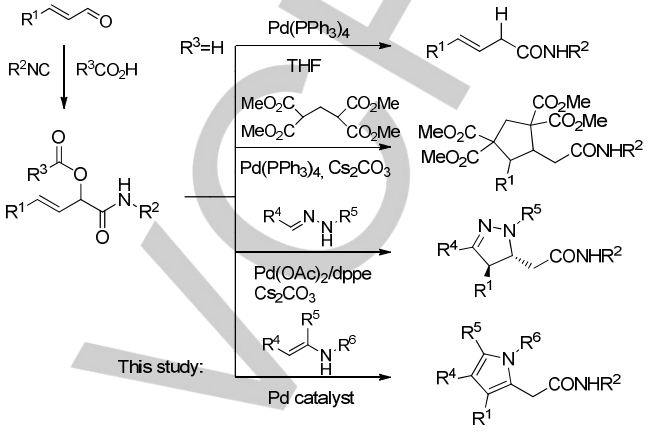
Abstract: The Passerini reaction of α,β-unsaturated aldehydes affords suitable substrates for a Tsuji-Trost reaction with NH-enamines. The latter behave as a 1,3-bisnucleophile leading to pyrrole derivatives with 5 points of diversity through a Tsuji-Trost/Michael addition/aromatization cascade.

Introduction

Isocyanides are mostly known in organic synthesis for their involvement in the Ugi and Passerini reactions.[1] Even though the Passerini coupling was discovered nearly forty years before its Ugi extension, it has been the object of a reduced number of studies probably due to its lower diversity and efficiency. Indeed, its three component nature together with a more difficult electrophilic activation of the aldehydes compared to their related imines in the Ugi reactions may explain the lower interest of the chemists community for this reaction.[2]
However, Passerini adducts has found interesting specific applications such as the potential transformations of the newly formed ester moiety as highlighted in the Passerini Amine Deprotection-Acyl Migration (PADAM) protocole.[3] Recently, we disclosed the use of Passerini adducts of cinnamaldehyde derivatives in various Tsuji-Trost reactions. Following a first Passerini/reduction cascade using formic acid as acidic component in the Passerini step,[4] we applied these Tsuji-Trost transformations of Passerini adducts to the formation of cyclic derivatives by the use of 1,3-bisnucleophiles such as bismalonates[5] or hydrazones (Scheme 1).[6] Stimulated by these results we now wish to present the use of enamines in a new approach toward pyrroles (Scheme 1).

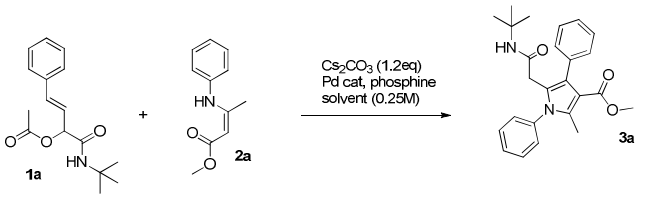
Results and Discussion

When 1,3 bis-malonates are used as nucleophiles in Tsuji-Trost reaction of cinnamaldehyde Passerini adducts, the synthetic sequence towards cyclopentane starts with a Tsuji-Trost addition at the γ position of the amide followed by an intramolecular Michael addition of the resulting α,β-unsaturated amide. In the case of *N*-arylhydrazones, a more complex cascade is settled taking advantage of the azaenamine behaviour of hydrazones. Enamines prepared from primary amines could behave as well as 1,3 bis-nucleophiles in a related strategy towards hydropyrroles.



Scheme 1. Tsuji-Trost reactions on Passerini adducts.

Tsuji-Trost type allylations of enamine derivatives have been the object of a limited number of studies mainly focused on enantioselective couplings. In the case of NH enamines, allylation with simple allylic derivatives was observed on the β-carbon nucleophilic position without any attack on nitrogen. To evaluate the feasibility of our project, we selected enamine **2a** obtained from methyl acetoacetate and aniline due to its stability and easy preparation under Lewis acid triggered conditions. When an equimolar mixture of **2a** and Passerini adduct **1a** (obtained from cinnamaldehyde, *tert*-butylisocyanide and acetic acid under solvent free conditions in 73 % yield) was treated with a $Pd(OAc)_2/PPh_3$ couple in toluene under microwave conditions, we observed the formation of the new pyrrole **3a** in moderate 54% isolated yield (Scheme 2).



$Pd(OAc)_2$ 5mol%, PPh_3 10mol%, toluene (120°C MW 30min) :	54%	$Pd(OAc)_2$ 5mol%, PPh_3 10mol%, toluene (110°C therm 30min) :	36%
$Pd(OAc)_2$ 5mol%, PPh_3 20mol%, toluene (120°C MW 30min) :	48%	$Pd(OAc)_2$ 5mol%, PCy_3 10mol%, toluene (120°C MW 30min) :	22%
$Pd(OAc)_2$ 5mol%, dppe 12mol%, toluene (120°C MW 30min) :	60%	$Pd(OAc)_2$ 5mol%, xantphos 5mol%, toluene (120°C MW 30min) :	57%
$Pd(OAc)_2$ 5mol%, dppe 5mol%, toluene (120°C MW 30min) :	65%	$Pd(OAc)_2$ 5mol%, dppe 5mol%, acetonitrile (120°C MW 30min) :	29%
$Pd_2(dba)_3$ 5mol%, PPh_3 10mol%, toluene (50°C therm 1h) :	10%	$Pd(OAc)_2$ 5mol%, dppe 10mol%, DMF (120°C MW 30min) :	22%

Scheme 2. Optimization toward the pyrrole **3a**.

At this stage of the study, the structure was proposed assuming a behavior close to the one observed in the Tsuji-Trost reaction of Passerini adduct **1a** with hydrazone. C13 and

[a] L. El Kaim, N. Narboni
Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA ParisTech- UMR 7652, Université Paris-Saclay, 828 Bd des Maréchaux, 91128 Palaiseau. France.
E-mail: laurent.elkaim@ensta-paristech.fr;

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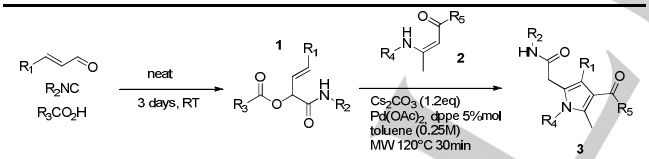
proton NMR data as well as NOESY experiments were not conclusive enough to conclude on the regioselectivity of the reaction between **1a** and **2a**. We went further on the optimization of reaction expecting that related compounds obtained later in the study would furnish better structural indications. Slightly lower temperature under thermal conditions (toluene reflux) gave a much lower yield as well as working at 50°C with a Pd_2dba_3/PPh_3 couple (Scheme 2). Changing the phosphine allowed to improve the reaction conditions with dppe giving the highest 65% yield. Surprisingly best yields were obtained with a slightly higher Pd/phosphine ratio than observed in the standard conditions for Tsuji-Trost type reactions. The use of $Pd(OAc)_2$ (5 mol%)/dppe (5 mol%) in toluene under microwave conditions at 120°C was finally selected for the examples performed with the various Passerini adducts **1** and enamines **2** displayed in Table 1.

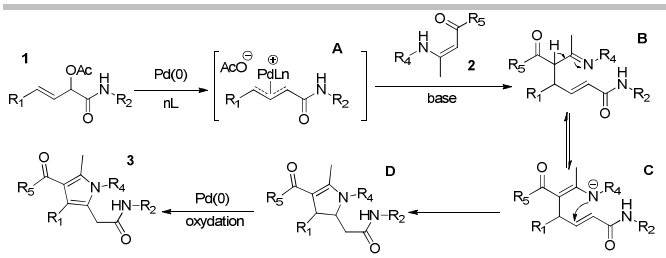
When acetic acid was replaced by pivalic acid (Table 1, entry 1), the resulting Passerini adduct **1a'** afforded pyrrole **3a** in comparable yield. However, as the first Passerini step was much less efficient with pivalic acid, acetic acid was preferred for all other examples. Overall, the yields are good to moderate. The reaction is not limited to enamines derived from anilines as shown by the formation of pyrroles **3f** and **3g** (Table 1, entries 6, 7) obtained from benzyl amine and thiophenylmethylamines. *Tert*-butyl isocyanide may be replaced by *p*-methoxybenzyl isocyanide leading to a slightly lower yield in the pyrrole formation (Table 1, entry 4). Various 3-aryl and heteroaryl pyrroles were obtained changing the aryl moiety of the cinnamaldehyde Passerini partner (Table 1, entries 2, 3, 5). Whereas β-ketoesters derived enamines afforded pyrroles in reasonable yields, β-diketones were not suitable for this cascade leading to poor yield of ketopyrrole (Table 1, entry 8). Rewardingly pyrrole **3f** gave us conclusive NOESY correlation between the two CH_2 groups of the molecule confirming the proposed structures for pyrroles **3a** to **3h**.

Table 1. Pyrrole synthesis through Tsuji-Trost/oxidation cascade.



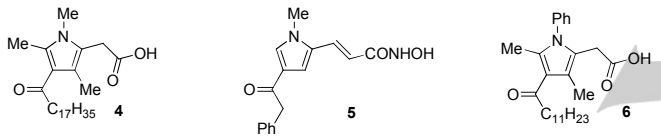
Entry	Passerini	Enamine	Pyrrole
1	**1a'** 30%	**2a** 89%	**3a** 63%
2	**1b** 81%	**2a** 89%	**3b** 61%
3	**1c** 39%	**2a** 89%	**3c** 60%
4	**1d** 87%	**2a** 89%	**3d** 48%
5	**1e** 63%	**2a** 89%	**3e** 35%
6	**1a** 73%	**2b** 72%	**3f** 51%
7	**1a** 73%	**2c** 89%	**3g** 44%
8	**1a** 73%	**2d** 91%	**3h** 19%

Following our previous reports on Tsuji-Trost reactions of Passerini adducts, we can propose a three-step mechanism for this new pyrrole formation from enamines (Scheme 3). Formation of palladium(0) is followed by the generation of a π-allyl palladium intermediate **A** from Passerini adduct **1**. The latter is attacked by the enamines **2** at the γ position of the amide as observed for malonate addition on the same compound. The resulting imine **B** rearrange to enamine **C** which undergo an intramolecular Michael addition to afford the dihydropyrrole **D**.[7] In opposition to what was observed in the Passerini conversion to dihydropyrazole, **D** is not stable in the medium and undergo a final oxidation to pyrrole **3** in agreement with similar redox processes observed in the literature.



Scheme 3. Proposed mechanism for the pyrrole formation.

Compared to indoles, their benzofused derivatives, the applications of pyrroles in medicinal chemistry may be considered rather limited. However pyrroles may be found in various natural compounds and many uses of pyrroles as anticancer, antitubercular or anti-inflammatory agents are reported in the literature.[8] In particular, families of pyrroles with similar structural patterns as the products prepared in our study have shown potential as cytosolic phospholipase A2 inhibitor (**4**, scheme 4),[9] histone deacetylase inhibitor (**5**, Scheme 4)[10] or prostaglandin synthetase inhibitor (**6**, Scheme 4).[11] Numerous synthetic approaches have been proposed for pyrroles since their first preparation at the end of the XIX century with enamines being key components as shown by their involvement in Hantzsch pyrrole synthesis.[12] Organometallic chemistry and palladium catalyzed process in particular are well represented among modern accesses to these scaffolds.[13]



Scheme 4. Some biologically relevant pyrrole derivatives.

Conclusion

As a conclusion, we have disclosed a new three-steps, one-pot synthesis of pyrroles starting from Passerini adduct and enamines derivatives. Both starting materials were prepared under neat conditions making the sequence even more appealing. Overall the process allow the preparation of pyrroles with five points of diversity, the scaffold obtained being close to some biologically relevant compounds. Further optimization will be required to raise the diversity of the enamine partner in particular for cyclohexanone derivatives which might afford an interesting route towards indoles.

Experimental Section

General Methods: Commercially available reagents and solvents were used without further purification. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance 300 and 400 MHz. Chemical shifts (δ) are reported in part per million (ppm) relative to internal TMS. High-Resolution Mass spectra (HRMS) were carried out with JEOL JMSGCmateII spectrometer. IR spectra were performed on a Perkin-Elmer FT 1600 spectrometer with wavelengths in cm^{-1}. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was performed using plates of silica 60 F_{254}. Melting points (Mp) were determined on a Stuart SMP3 apparatus and were left uncorrected. Products 1a,[5] 1c,[5] 1d,[5] have been prepared following the procedure described in the literature as well as 2a,[14] 2b[14], and 2d[14].

General procedure A for Passerini reaction:[5] A mixture of aldehyde (1.0 equiv), acid (1.0 equiv) and isocyanide (1.0 equiv) was stirred under argon at room temperature for 2 days. The crude was purified by flash chromatography on silica gel.

General procedure B for enamine synthesis:[14] A mixture of carbonyle derivative (1.0 equiv), amine (1.0 equiv) and zinc triflate (20 mol%) was stirred at room temperature for 15min. the crude was purified by flash chromatography on silica gel with AcOEt/EP (20/80) as eluant.

General procedure C for pyrrole synthesis: To a 0.25 M solution of Passerini adduct **1** (1.0 equiv) in toluene were added enamine **2** (1.0 equiv), Cs_2CO_3 (1.2 equiv), dppe (5 mol%) and $Pd(OAc)_2$ (5 mol%). The resulting mixture was hated under microwave at 120°C during 30 minutes The solvent was removed afterwards under reduced pressure and the crude was purified by flash chromatography on silica gel.

(E)-1-(*tert*-butylamino)-1-oxo-4-phenylbut-3-en-2-yl pivalate (1a'): Compound **1a'** was prepared according to general procedure A starting from 264mg (2mmol, 1equiv) trans-cinnamaldehyde, 1equiv (2mmol) *tert*-butyl isocyanide and 1equiv (2mmol) pivalic acid. Purification by flash chromatography with a gradient AcOEt/EP (10/90 to 30/70) gave the desired product (190mg, 30%) as a white solid. **Mp** 110°C ; **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.44 (d, J = 7.6 Hz, 2H, HAr), 7.36 (t, J = 7.4 Hz, 2H, HAr), 7.31 (d, J = 5.6 Hz, 1H, HAr), 6.73 (d, J = 16.1 Hz, 1H), 6.35 (dd, J = 16.0, 6.3 Hz, 1H), 5.95 (s, 1H, NH), 5.71 (d, J = 6.3 Hz, 1H), 1.42 (s, 9H, tBu(C=O)), 1.35 (s, 9H, tBuNH) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 176.42 (Cq, OC=O), 167.42 (Cq, NC=O), 135.88 (Cq, CAr), 133.78 (CH), 128.59 (2CH, CAr), 128.29 (CH, CAr), 126.83 (2CH, CAr), 123.04 (CH), 74.17 (CH), 51.41 (Cq, tBu(C=O)), 38.89 (Cq, tBuNH) 28.72 ($3CH_3$, tBu(C=O)), 27.16 ($3CH_3$, tBuNH) ; **IR (ν, cm^{-1})** 3320, 2967, 1731, 1668, 1518, 1478, 1450, 1393, 1364, 1272, 1223, 1126, 964 ; **HRMS (EI)** Calcd. for $C_{19}H_{27}NO_3$: 317.1991 found : 317.1979

(E)-1-(*tert*-butylamino)-4-(furan-2-yl)-1-oxobut-3-en-2-yl acetate (1b): Compound **1b** was prepared according to general procedure A starting from 366mg (3mmol, 1equiv) (2E)-3-(furan-2-yl)prop-2-enal, 1equiv (3mmol) *tert*-butyl isocyanide and 1equiv (3mmol) acetic acid. Purification by flash chromatography with a gradient AcOEt/EP (10/90 to 30/70) gave the desired product (643mg, 81%) as a brown solid. **Mp** 119 - 120°C ; **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.36 (s, 1H, HFur), 6.53 (d, J = 15.8 Hz, 1H), 6.37 (s, 1H), 6.32 (s, 1H), 6.15 (dd, J = 15.8, 7.0 Hz, 1H), 5.82 (s, 1H, NH), 5.58 (d, J = 7.0 Hz, 1H), 2.19 (s, 3H, Me), 1.37 (s, 9H, tBu) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 169.2 (Cq, OC=O), 167.0 (Cq, NC=O), 151.4 (Cq), 142.7 (CH), 122.8 (CH), 121.1 (CH), 111.5 (CH), 109.8 (CH), 74.5 (CH), 51.6 (Cq, tBu), 28.7 ($3CH_3$, tBu), 21.1 (CH_3, Me) ; **IR (ν, cm^{-1})** 3291, 3080, 2966, 1741, 1661, 1487, 1364, 1218, 1012, 959 ; **HRMS (EI)** Calcd. for $C_{14}H_{19}NO_4$: 265.1314 found : 265,1310

(E)-1-(*tert*-butylamino)-4-(2-nitrophenyl)-1-oxobut-3-en-2-yl acetate (1e): Compound **1e** was prepared according to general procedure A starting from 354mg (2mmol, 1equiv) of (2E)-3-(2-nitrophenyl)prop-2-enal 1equiv (2mmol) of *tert*-butyl isocyanide and 1equiv (2mmol) of acetic acid Purification by flash chromatography with a gradient AcOEt/EP (10/90 to 30/70) gave the desired product (403mg, 63%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.98 (d, J = 8.3 Hz, 1H, HAr), 7.67 - 7.56 (m, 2H, HAr), 7.49 - 7.37 (m, 1H, HAr), 7.15 (d, J = 15.9 Hz, 1H), 6.33 (dd, J = 15.9, 5.9 Hz, 1H), 5.93 (s, 1H, NH), 5.69 (d, J = 5.9 Hz, 1H), 2.24 (s, 3H, Me), 1.38 (s, 9H, tBu) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 169.16 (Cq, OC=O), 166.47 (Cq, NC=O), 147.73 (Cq, CAr), 133.46 (CH, CAr), 131.87 (Cq, CAr), 129.07 (CH, CAr), 128.83 (CH, CAr), 128.71 (CH), 128.58 (CH), 124.74 (CH, CAr), 73.89 (CH), 51.76 (Cq, tBu), 28.68 ($3CH_3$, tBu), 21.03 (CH_3, Me) ; **IR (ν, cm^{-1})** 3312, 3073, 2969, 1742, 1666, 1519, 1343, 1217, 1100, 1042, 965 ; **HRMS (EI)** Calcd. for $C_{16}H_{20}N_2O_5$: 320.1372 found : no pic found

(Z)-methyl 3-((thiophen-2-ylmethyl)amino)but-2-enoate (2c): Compound **2c** was prepared according general procedure B starting from 323µL (3mmol, 1 equiv) of methyl acetoacetate and 1equiv (3mmol) 2-

thenylamine. Purification afforded 562mg of colorless oil (89% yield). **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 8.90 (s, 1H, NH), 7.22 (d, J = 4.3 Hz, 1H), 6.94 (s, 2H), 4.58 (d, J = 6.2 Hz, 2H, CH_2), 4.54 (s, 1H), 3.63 (s, 3H, OMe), 1.97 (s, 3H, Me) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 170.8 (Cq, C=O), 161.2 (Cq), 142.0 (Cq), 127.0 (CH), 124.9 (CH), 124.8 (CH), 83.4 (CH), 50.09 (CH_3, OMe), 42.08 (CH_2), 19.31 (CH_3, Me) ; **IR (ν, cm^{-1})** 3289, 3104, 2945, 1650, 1595, 1433, 1238, 1169, 1096, 1007, 929 ; **HRMS (EI)** Calcd. for $C_{10}H_{13}NO_2S$: 211.0667 found : 211.0666

Methyl 5-(2-(*tert*-butylamino)-2-oxoethyl)-2-methyl-1,4-diphenyl-*1H*-pyrrole-3-carboxylate (3a): Compound **3a** was prepared according general procedure C starting from 100mg (0.36mmol, 1equiv) of **1a** and 1equiv (0.36mmol) of **2a**. Purification by flash chromatography with a gradient Et_2O/EP (10/90 to 30/70) gave the desired product (96mg, 65%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.54 - 7.45 (m, 3H), 7.41 - 7.28 (m, 6H), 7.24 (s, J = 6.4 Hz, 1H), 5.07 (s, 1H), 3.62 (s, 3H), 3.14 (s, 2H), 2.32 (s, 3H), 1.16 (s, 9H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 168.33 (Cq), 166.11 (Cq), 137.31 (Cq), 136.91 (Cq), 135.51 (Cq), 130.08 (2CH), 129.63 (2CH), 129.20 (CH), 128.52 (2CH), 127.91 (2CH), 126.69 (CH), 125.05 (Cq), 124.98 (Cq), 111.27 (Cq), 51.07 (Cq), 50.65 (CH_3), 34.08 (CH_2), 28.53 ($3CH_3$), 12.90 (CH_3) ; **IR (ν, cm^{-1})** 3335, 3055, 2963, 1655, 1505, 1448, 1363, 1264, 1240, 1221, 1193, 1082 ; **HRMS (EI)** Calcd. for $C_{25}H_{28}N_2O_3$: 404.2100 found : 404,2107

Methyl 5-(2-(*tert*-butylamino)-2-oxoethyl)-4-(furan-2-yl)-2-methyl-1-phenyl-*1H*-pyrrole-3-carboxylate (3b): Compound **3b** was prepared according general procedure C starting from 100mg (0.38mmol, 1equiv) of **1b** and 1equiv (0.38mmol) of **2a**. Purification by flash chromatography with a gradient Et_2O/EP (10/90 to 30/70) gave the desired product (90mg, 61%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.54 - 7.47 (m, 3H), 7.46 (dt, J = 7.1, 3.5 Hz, 1H), 7.23 - 7.15 (m, 2H), 6.50 - 6.45 (m, 2H), 5.42 (s, 1H), 3.76 (s, 3H), 3.25 (s, 2H), 2.28 (s, 3H), 1.22 (s, 9H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 168.24 (Cq), 165.64 (Cq), 148.27 (Cq), 141.55 (CH), 137.60 (Cq), 136.50 (Cq), 129.73 (2CH), 129.43 (CH), 128.35 (2CH), 127.25 (Cq), 114.14 (Cq), 111.16 (Cq), 110.97 (CH), 108.97 (CH), 51.12 (Cq), 51.01 (CH_3), 34.99 (CH_2), 28.58 ($3CH_3$), 12.91 (CH_3) ; **IR (ν, cm^{-1})** 3328, 2926, 1661, 1498, 1392, 1416, 1364, 1222, 1085 ; **HRMS (EI)** Calcd. for $C_{23}H_{26}N_2O_4$: 394.1893 found : 394,1900

Methyl 5-(2-(*tert*-butylamino)-2-oxoethyl)-4-(4-methoxyphenyl)-2-methyl-1-phenyl-*1H*-pyrrole-3-carboxylate (3c): Compound **3c** was prepared according general procedure C starting from 100mg (0.33mmol, 1 equiv) of **1c** and 1equiv (0.33mmol) of **2a**. Purification by flash chromatography with a gradient Et_2O/EP (10/90 to 30/70) gave the desired product (86mg, 60%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.45 - 7.39 (m, 3H), 7.19 - 7.15 (m, 4H), 6.87 - 6.82 (m, 1H), 5.02 (s, 1H), 3.77 (s, 3H), 3.57 (s, 3H), 3.07 (s, 2H), 2.25 (s, 3H), 1.10 (s, 9H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 168.41 (Cq), 166.15 (Cq), 158.41 (Cq), 137.15 (Cq), 136.99 (Cq), 131.14 (2CH), 129.60 (2CH), 129.15 (CH), 128.51 (2CH), 127.68 (Cq), 125.06 (Cq), 124.63 (Cq), 113.38 (2CH), 111.31 (Cq), 55.27 (CH_3), 51.05 (Cq), 50.65 (CH_3), 34.11 (CH_2), 28.56 ($3CH_3$), 12.95 (CH_3) ; **IR (ν, cm^{-1})** 3331, 3061, 2963, 1656, 1439, 1392, 1363, 1288, 1241, 1160, 1082, 1029 ; **HRMS (EI)** Calcd. for $C_{26}H_{30}N_2O_4$: 434.2206 found : 434,2195

Methyl 5-(2-((4-methoxybenzyl)amino)-2-oxoethyl)-2-methyl-1,4-diphenyl-*1H*-pyrrole-3-carboxylate (3d): Compound **3d** was prepared according general procedure C starting from 100mg (0.29mmol, 1 equiv) of **1d** and 1equiv (0.29mmol) of **2a**. Purification by flash chromatography with a gradient AcOEt/EP (10/90 to 20/80) gave the desired product (66mg, 48%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.37 (d, J = 6.2 Hz, 2H), 7.27 - 7.15 (m, 6H), 7.07 (d, J = 7.4 Hz, 2H), 6.97 (d, J = 7.2 Hz, 2H), 6.77 (d, J = 7.0 Hz, 2H), 5.53 (s, 1H), 4.12 (d, J = 5.5 Hz, 2H), 3.74 (s, 3H), 3.53 (s, 3H), 3.19 (s, 2H), 2.21 (s, 3H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 169.13 (Cq), 166.00 (Cq), 159.08 (Cq), 137.50 (Cq), 136.76 (Cq), 135.20 (Cq), 129.99 (2CH), 129.70 (2CH), 129.36 (2CH), 129.23 (Cq), 128.40 (2CH), 127.91 (2CH), 126.73 (CH), 125.42 (Cq), 124.33 (CH), 114.12 (Cq), 114.01 (2CH), 111.40 (Cq), 55.38 (CH_3), 50.67 (CH_3), 43.12 (CH_2), 33.08 (CH_2), 12.83 (CH_3) ; **IR (ν, cm^{-1})** 3301, 2931, 1660, 1511, 1447, 1287, 1244, 1159, 1083, 1033 ; **HRMS (EI)** Calcd. for $C_{27}H_{32}N_2O_4$: 468.2049 found : 468,2060

Methyl 5-(2-(*tert*-butylamino)-2-oxoethyl)-2-methyl-4-(2-nitrophenyl)-1-phenyl-*1H*-pyrrole-3-carboxylate (3e): Compound **3e** was prepared according general procedure C starting from 100mg (0.31mmol, 1 equiv) of **1e** and 1equiv (0.31mmol) of **2a**. Purification by flash chromatography with a gradient Et_2O/EP (10/90 to 30/70) gave the desired product (51mg, 35%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 8.06 (d, J = 9.1 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.54 - 7.45 (m, 4H), 7.39 - 7.32 (m, 2H), 7.25 - 7.24 (m, 1H), 5.75 (s, 1H), 3.55 (s, 3H), 3.22 (dd, J = 132.8, 17.3 Hz, 2H), 2.33 (s, 3H), 1.17 (s, 9H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 167.98 (Cq), 165.16 (Cq), 150.22 (Cq), 138.38 (Cq), 136.45 (Cq), 133.02 (CH), 132.97 (CH), 130.91 (Cq), 129.85 (CH), 129.69 (CH), 129.52 (CH), 128.53 (CH), 128.27(CH), 128.15(CH), 124.51 (Cq), 124.27(CH), 121.20 (Cq), 110.21 (Cq), 51.31 (Cq), 50.73 (CH_3), 34.15 (CH_2), 28.47 ($3CH_3$), 12.93 (CH_3) ; **IR (ν, cm^{-1})** 3328, 2965, 1700, 1658, 1525, 1450, 1362, 1280, 1225, 1194, 1162, 1093 ; **HRMS (EI)** Calcd. for $C_{25}H_{27}N_3O_5$} : 449.1951 found : 449.1938

Methyl 1-benzyl-5-(2-(*tert*-butylamino)-2-oxoethyl)-2-methyl-4-phenyl-*1H*-pyrrole-3-carboxylate (3f): Compound **3f** was prepared according general procedure C starting from 100mg (0.36mmol, 1 equiv) of **1a** and 1equiv (0.36mmol) of **2b**. Purification by flash chromatography with a gradient Et_2O/EP (10/90 to 30/70) gave the desired product (77mg 51%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.40 - 7.21 (m, 8H), 6.93 (d, J = 7.4 Hz, 2H), 5.27 (s, 2H, CH_2), 5.02 (s, 1H), 3.58 (s, 3H) 3.20 (s, 2H), 2.51 (s, 3H), 1.15 (s, 9H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 168.78 (Cq), 166.08 (Cq), 136.74 (Cq), 136.67 (Cq), 136.01 (Cq), 130.24 (2CH), 129.00 (2CH), 127.91 (2CH), 127.57 (CH), 126.69 (CH), 125.65 (2CH), 125.04 (Cq), 124.52 (Cq), 111.10 (Cq), 51.22 (CH_3), 50.56 (Cq), 47.29 (CH_2), 34.05 (CH_2), 28.53 ($3CH_3$), 11.81 (CH_3) ; **IR (ν, cm^{-1})** 3330, 2965, 1651, 1527, 1448, 1267, 1225, 1162, 1095, 1069 ; **HRMS (EI)** Calcd. for $C_{26}H_{30}N_2O_3$: 418.2256 found : 418,2258

Methyl 5-(2-(*tert*-butylamino)-2-oxoethyl)-2-methyl-4-phenyl-1-(thiophen-2-ylmethyl)-*1H*-pyrrole-3-carboxylate (3g): Compound **3g** was prepared according general procedure C starting from 100mg (0.36mmol, 1 equiv) of **1a** and 1equiv (0.36mmol) of **2c**. Purification by flash chromatography with a gradient Et_2O/EP (10/90 to 30/70) gave the desired product (68mg, 44%) as a yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.36 (t, J = 7.2 Hz, 2H), 7.30 (d, J = 7.3 Hz, 1H), 7.25 - 7.20 (m, 3H), 6.94 (dd, J = 5.1, 3.5 Hz, 1H), 6.81 - 6.73 (m, 1H), 5.40 (s, 2H), 5.01 (s, 1H), 3.57 (s, 3H), 3.30 (s, 2H), 2.61 (s, 3H), 1.17 (s, 9H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 168.79 (Cq), 165.98 (Cq), 139.80 (Cq), 136.23 (Cq), 135.94 (Cq), 130.24 (2CH), 128.77 (Cq), 127.89 (2CH), 127.14 (CH), 126.71 (CH), 125.21 (CH), 125.04 (CH), 124.15 (Cq), 111.29 (Cq), 51.25 (Cq), 50.56 (CH_3), 43.19 (CH_2), 34.05 (CH_2), 28.54 ($3CH_3$), 11.83 (CH_3) ; **IR (ν, cm^{-1})** 3341, 2963, 1655, 1526, 1449, 1408, 1364, 1194, 1070 ; **HRMS (EI)** Calcd. for $C_{24}H_{28}N_2O_3S$: 424.1821 found : 424,1824

2-(4-acetyl-5-methyl-1,3-diphenyl-*1H*-pyrrol-2-yl)-N-(*tert*-butyl)acetamide (3h): Compound **3h** was prepared according general procedure C starting from 100mg (0.36mmol, 1 equiv) of **1a** and 1equiv (0.36mmol) of **2d**. Purification by flash chromatography with a gradient Et_2O/EP (10/90 to 30/70) gave the desired product (27mg, 20%) as yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz) (δ, ppm)** 7.42 (d, J = 6.3 Hz, 2H), 7.37 - 7.25 (m, 6H), 7.19 (d, J = 6.2 Hz, 2H), 4.96 (s, 1H), 3.03 (s, 2H), 2.22 (s, 3H), 1.86 (s, 3H), 1.10 (s, 9H) ; **^{13}C-NMR ($CDCl_3$, 100.6 MHz) (δ, ppm)** 197.35 (Cq), 168.33 (Cq), 136.79 (Cq), 136.38 (Cq), 135.99 (Cq), 130.32 (2CH), 129.63 (2CH), 129.18 (CH), 128.62 (2CH), 128.44 (2CH), 127.31 (CH), 124.79 (Cq), 124.61 (Cq), 122.04 (Cq), 51.13 (Cq), 34.01 (CH_2), 31.05 (CH_3), 28.56 ($3CH_3$), 13.11 (CH_3) ; **IR (ν, cm^{-1})** 3315, 3060, 2963, 2925, 1650, 1496, 1362, 1224, 1157, 1028, 954 ; **HRMS (EI)** Calcd. for $C_{25}H_{28}N_2O_2$: 388.2151 found : 388,2139

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Keywords: pyrrole • Passerini • Tsuji-Trost • enamine • multicomponent

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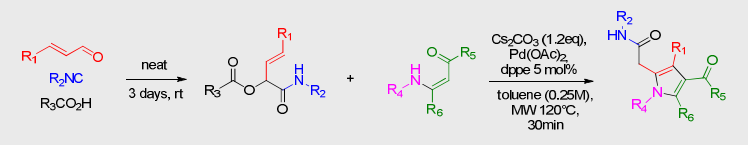

Multicomponent reactions

Laurent El Kaim, Noisette Narboni

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Passerini/Tsuji-Trost strategy towards pyrroles derivatives

New Tsuji-Trost coupling between Passerini adducts and enamines: multicomponent access to pyrroles presenting five points of variation.

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