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Pyridazine derivatives. Part 38: Efficient Heck alkenylation at position 5 of the 6-phenyl-3(2*H*)-pyridazinone system ☆

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Abstract—Several 6-phenyl-3(2*H*)-pyridazinones bearing different alkenyl groups at position 5 have been prepared in the search for novel antiplatelet agents. The target compounds were synthesised by a palladium-catalysed Heck cross-coupling reaction. Variable amounts of 4-phenyl-6-substituted-2-phthalazinones were isolated as by-products during these experiments. The crucial issues for successful Heck coupling in these systems concern the protection of position 2 of the heterocyclic ring and the use of tris(*o*-tolyl)phosphine as a ligand.
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Low molecular weight heterocycles have gained a central role in the high throughput synthesis of libraries of drug-like compounds.[1] The tremendous variety of naturally occurring heterocycles and their wide range of biological activities continue to encourage the development of elegant and efficient synthetic routes to these substances.[2] In this context, the significant pharmacological activities described for pyridazine derivatives in recent decades[3] have inspired researchers from academia and industry to explore the usefulness of this heterocyclic template in the search for new drugs. As a consequence, the considerable efforts directed towards the synthesis of these derivatives have allowed the development of new promising entities that act on numerous important targets.[4]

In recent years we have been involved in developing novel pyridazinone-based antiplatelet agents.[5] For example, we recently reported the antiplatelet activity of compounds **I**[6] (Fig. 1, X = CHO, COR, COOR, CN, OR) and the discovery of several 5-alkylidene-6-phenyl-3(2*H*)-pyridazinones **III** (Fig. 1, X = COOR, CN, COR), which represent a new family of potent antiplatelet agents.[7] In an effort to elucidate structure–activity relationships for this type of derivative we became interested in preparing the 5-alkenyl-6-phenyl-3(2*H*)-pyridazinones **II** (Fig. 1, X = COOR, COR, CN), which can be considered as vinyl analogues of **I** and/or simple derivatives of **III**.

All possible retrosynthetic schemes to access the target compounds **II**, starting from precursors of type **I**, require one C–C bond disconnection. A first approach could involve Wittig condensation of phosphorus ylides with the appropriate 5-formyl derivative, but this route is limited by the synthetic accessibility of the required heterocyclic carbaldehyde.[8] The second option is to

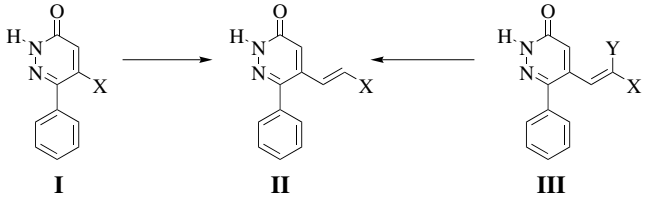

Figure 1.

Keywords: Pyridazinones; Heck coupling; Phthalazinones.

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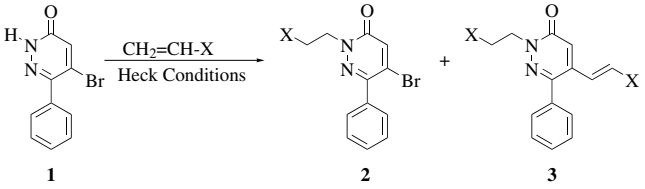
carry out the well-established Heck reaction[9] on the readily obtained 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1**.[10] Palladium-catalysed cross-coupling reactions in heterocyclic chemistry,[11] and especially in pyridazine chemistry,[12] have become widely studied in recent years but curiously very few references describe Heck olefinations on a 1,2-diazine.[13]

As a continuation of our work into the development of new and versatile palladium-assisted syntheses of pharmacologically useful pyridazinones, we describe here the preliminary results obtained during the study the scope and limitations of a Heck alkenylation methodology as a simple entry to 5-functionalised pyridazinones and phthalazinones.

Initial experiments were performed using 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1** with a slight excess (1.5 equiv) of ethyl acrylate as a model reaction under the classical Heck conditions[9] (Scheme 1).[14] Despite the fact that various catalytic systems were used [e.g., $Pd[Ph_3]_4$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$ or $Pd(OAc)_2$ in combination with $P(Ph)_3$, P(2-tolyl)$_3$, dppe, bases (Et_3N, Na_2CO_3, NaOAc) and solvents (acetonitrile, toluene, DMF)], all attempts to obtain the desired 5-alkenyl-6-phenyl-3(2*H*)-pyridazinones **8** from **1** failed and a variable mixture of compounds **2**[15] and **3**[16] was always isolated (Scheme 1, Table 1).



1 **2** **3**

Scheme 1. Heck conditions: method A: $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 120 °C, sealed tube; method B: $PdCl_2(PPh_3)_2$, Et_3N, DMF, 120 °C, sealed tube.

Table 1

Entry	X	Yield (%) of **2**[a]	Yield (%) of **3**[a]
1	COOEt	70	20
2	COOMe	63	15
3	CN	65	18
4	Ph	—	—

[a] Reported yield corresponds to data obtained using method A.

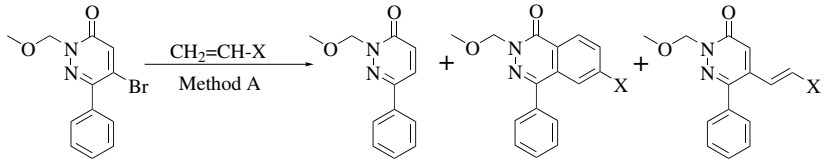
The formation of 2-substituted-3-pyridazinones **2** can be rationalised in terms of a Michael addition between the 3(2*H*)-pyridazinone and the highly activated sterically unhindered ethyl acrylate.[17] Other typical Michael acceptors such as acrylonitrile, methyl acrylate or butenone reacted similarly. Analogous experiments using styrene (a nonactivated olefin) led to recovery of unreacted pyridazinone **1**.The reactivity of **1** toward Heck alkenylation (Scheme 1) is not dissimilar to that described in previous works on palladium-catalysed reactions of pyridazinones[18] and confirms the advantages of protecting position 2 of the heterocyclic ring before performing cross-coupling reactions.

Isolation of compounds **3** under these conditions (Scheme 1) can be explained by subsequent Heck alkenylation at position 5 of compounds **2** (once the tautomeric carbonyl group at position 3 has been blocked as a consequence of the Michael addition). The low yields obtained for compounds **3** (including the case where a larger excess of acrylate (2.5–3 equiv) was used) could suggest that the catalytic system employed is not optimal for such a transformation.

The drawback outlined above was circumvented by blocking position 2 of compound **1** by the introduction of a methoxymethyl (MOM) group.[18] We then proceeded to study the palladium-catalysed Heck alkenylation of **4** (Scheme 2).

Treatment of **4** with ethyl acrylate (2 equiv), PPh_3 as ligand, Et_3N as base and $Pd(OAc)_2$ as the palladium source in DMF led to the formation of debrominated pyridazinone **5** (50%) along with a very small amount of the desired 5-alkenyl-3-pyridazinone **7a** (10%) (Scheme 2). Surprisingly, a compound that was identified as the phthalazinone **6a** (28%) was also isolated from the reaction mixture (Scheme 2). Analogous results were obtained on applying these conditions to different olefins (Table 2), with compound **5** (45–50%) and phthalazinones **6** isolated in yields in the range 25–30%. It is noteworthy that during these experiments, the use of styrene as the alkene component did not lead to the formation of the corresponding phthalazinone.

The structures of compounds **5**, **6** and **7** were unambiguously established on the basis of their analytical and spectroscopic data.[20] The unexpected phthalazinones **6** were also completely characterised by NMR experiments and by single crystal X-ray analysis of compound **6a** (Fig. 2).[21]



4 **5** **6a X = COOEt** **7a X = COOEt**
6b X = COOMe **7b X = COOMe**
6c X = CN **7c X = CN**

Scheme 2. Reagents and conditions: method A: $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 120 °C, sealed tube.[19]

Table 2

Entry	Olefin	Yield (%) of **5**	Yield (%) of **6**	Yield (%) of **7**
1	CH_2=CHCOOEt	50	28	10
2	CH_2=CHCOOMe	45	25	8
3	CH_2=CHCN	48	30	10
4	CH_2=CHPh	65	—	5

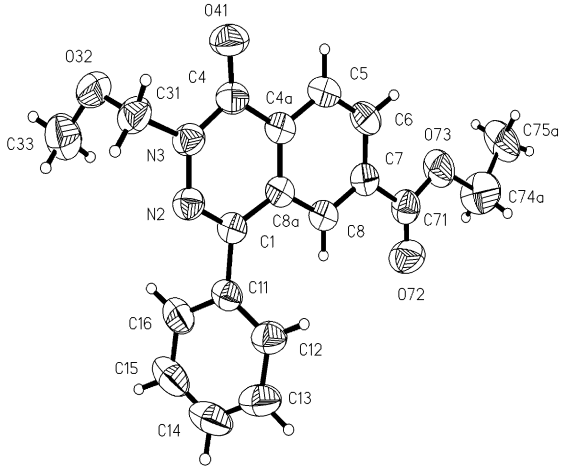


Figure 2. ORTEP diagram of compound **6a**, obtained by single crystal X-ray diffraction, showing the molecular conformation and numbering scheme.

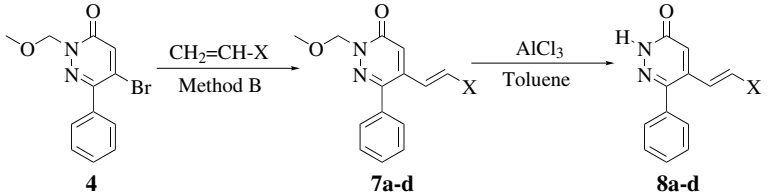
The unexpected isolation of phthalazinones **6** under these conditions is a very interesting finding and could open a new entry to functionalised phthalazinones starting form 5-substituted-3-pyridazinones. The established structures of compounds **6** (with the X group at position 6 of the phthalazinone ring) suggest that a highly regioselective processes could be operating during their formation. Preliminary mechanistic proposals to explain phthalazinone formation are based on a tandem reaction. This process would initially involve a Heck sp^2 cascade due to a second insertion of another olefin molecule into the previously formed σ-alkylpalladium complex, which could be arylated through intramolecular C–H activation (to yield palladacycle intermediates). The final steps in the proposed sequence are reductive elimination, oxidative addition, β-elimination and then aromatisation to yield compounds **6**. The excellent results obtained have led us to carry out new experiments aimed at improving the yields of phthalazinones **6** and these are currently under way.

Since we were unable to prepare target compounds **7** by the procedures described above, a detailed study of this transformation was initiated. The fact that debrominated pyridazinone **5** was obtained as the main product during Heck alkenylation of **4** suggests that migratory insertion of the olefin to the σ-heteroarylpalladium(II) complex is not a favoured process. For this reason experiments were aimed at finding appropriate conditions to accelerate the olefin migratory insertion. Pyridazinone **4** was used as the electrophile and the Heck reaction was performed using different catalysts, phosphines and solvents from the plethora of protocols and catalytic systems described for the successful Heck alkenylation.[9] The ultimate aim was to find optimal experimental conditions to obtain compounds **7**.

These screening experiments revealed that the formation of debrominated pyridazinone **5** and phthalazinone **6** is usually associated with the presence of acetates in the coupling cocktails (provided by the palladium acetate). Indeed, the use of catalytic systems that did not contain these anions [e.g., $Pd_2(dba)_3$ and $Pd(Ph_3)_2Cl_2$] gave the expected 5-alkenyl-3-pyridazinones **7** in moderate yields (35–50%) and the formation of compounds **5** and **6** was minimal. Although the role of acetate proved to be critical in the coupling behaviour, another important issue that needed to be taken into account was the phosphine; it was observed that the nature of the phosphine can dramatically change the results obtained in reactions performed in the presence of acetates. For instance, replacement of triphenylphosphine by the bulky tris(*o*-tolyl)phosphine [$PdCl_2[P(o\text{-tolyl})_3]_2$ or $Pd(OAc)_2$/$P(o\text{-tolyl})_3$] in cocktails generated a remarkable increase in the yield (50–70%) of the 5-alkenyl-3-pyridazinones **7**. Our choice for the coupling experiments on **4** therefore involved heating in DMF in the presence of 5% $PdCl_2P[(o\text{-tolyl})_3]_2$ with 2 equiv of triethylamine. The application of these optimised conditions[22] to a variety of olefins gave the corresponding 5-alkenyl-6-phenyl-2-methoxymethyl-3-pyridazinones **7a**–**d**[23] in moderate to good yields (Scheme 3, Table 3).

Table 3

Compound	X	Yield (%) of **7**	Deprotection (HCl) Yield (%)
7a	COOEt	73	75
7b	COOMe	70	78
7c	CN	40	77
7d	Ph	50	70



Scheme 3. Reagents and conditions: method B: $PdCl_2[P(o\text{-tolyl})_3]_2$, Et_3N, DMF, 120 °C, sealed tube.[22]

Cleavage of the methoxymethyl group at position 2 in **7** was successfully performed using 6 N HCl or, alternatively, under mild conditions by employing aluminium chloride[24] to obtain the target 5-alkenyl-6-phenyl-3(2*H*)-pyridazinones **8**[25] (Scheme 3, Table 3).

In summary, we have developed a straightforward palladium-catalysed route to several pharmacologically interesting 5-alkenyl-6-phenyl-3(2*H*)-pyridazinones **8**. The crucial points for the successful Heck coupling in this series concern the protection of position 2 of the heterocyclic ring and the use of tris(*o*-tolyl)phosphine as ligand. Further investigations into the application of the Heck reaction as an alternative synthetic entry to substituted phthalazinones and the study of the antiplatelet activity of the resulting compounds are in progress.

Acknowledgements

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References and notes

1. Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, *10*, 1471; Ugi, I.; Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647.
2. Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
3. Frank, H.; Heinisch, G. Pharmacologically Active Pyridazines. In *Progress in Medicinal Chemistry. Part 1*; Ellis, G. P., West, G. B., Eds.; Elsevier: Amsterdam, 1990; 27, p 1; Frank, H.; Heinisch, G. Pharmacologically Active Pyridazines. Part 2. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: Amsterdam, 1992; 29, p 141.
4. Li, C. S.; Brideau, C.; Chan, C. C.; Savoie, C.; Claveau, D.; Charleston, S.; Gordon, R.; Greig, G.; Gauthier, J. Y.; Lau, K.; Riendeau, D.; Thierien, M.; Wong, E.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 597; Giovannoni, M. P.; Vergelli, C.; Ghelardini, C.; Galeotti, N.; Bartolini, A.; Dal Piaz, V. *J. Med. Chem.* **2003**, *46*, 1055; Costantino, L.; Rastelli, G.; Gamberini, M. C.; Giovannoni, M. P.; DalPiaz, V.; Vianello, P.; Barlocco, D. *J. Med. Chem.* **1999**, *42*, 1894; Matyus, P. *J. Heterocycl. Chem.* **1998**, *35*, 1075; Mylari, B. L.; Armento, S. J.; Beebe, D. A.; Conn, E. L.; Coutcher, J. B.; Dina, M. S.; OáGorman, M. J.; Linhares, M. C.; Martin, W. H.; Oates, P. J.; Tess, D. A.; Withbroe, G. J.; Zembrowski, W. J. *J. Med. Chem.* **2003**, *46*, 2283.
5. Montero-Lastres, A.; Fraiz, N.; Cano, E.; Laguna, R.; Estévez, I.; Raviña, E. *Acta Pharm. Hung.* **1999**, *22*, 1376.
6. Laguna, R.; Rodriguez-Liñares, B.; Cano, E.; Estévez, I.; Raviña, E.; Sotelo, E. *Chem. Pharm. Bull.* **1997**, *45*, 1151; Sotelo, E.; Fraiz, N.; Yañez, M.; Terrades, V.; Laguna, R.; Cano, E.; Raviña, E. *Bioorg. Med. Chem.* **2002**, *10*, 2873.
7. Sotelo, E.; Fraiz, N.; Yañez, M.; Brea, J. M.; Laguna, R.; Cano, E.; Raviña, E. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 1575.
8. Sotelo, E.; Raviña, E.; Estévez, I. *J. Heterocycl. Chem.* **1999**, *36*, 985; Sotelo, E., Ph.D. Thesis; University of Santiago de Compostela, Spain, 2000.
9. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, 3009; Brase, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; p 99; Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2; de Meijere, A.; Meyer, F. E. *Angew Chem. Int. Ed. Engl.* **1994**, *33*, 2379.
10. Estévez, I.; Raviña, E.; Sotelo, E. *J. Heterocyclic. Chem.* **1998**, *35*, 1421.
11. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Elsevier: Amsterdam, 2000; p 3.
12. Riedl, Z.; Maes, B. U. W.; Monsieurs, K.; Lemiere, G. L. F.; Matyus, P.; Hajós, G. *Tetrahedron* **2002**, *58*, 5645; Kosmrlj, J.; Maes, B. U. W.; Lemiere, G. L. F.; Haemers, H. *Synlett* **2000**, *11*, 1581; R'kyek, O.; Maes, B. U. W.; Jonkers, T. H. M.; Lemiere, G. L. F.; Dommisse, R. A. *Tetrahedron* **2001**, *57*, 10009; Coelho, A.; Raviña, E.; Sotelo, E. *Synlett* **2002**, 6062; Sotelo, E.; Coelho, A.; Raviña, E. *Tetrahedron Lett.* **2003**, *44*, 4459; Bourotte, M.; Pellegrini, N.; Schmitt, M.; Bourginon, J. J. *Synlett* **2003**, 1482; Guerry, S.; Parrot, I.; Rival, Y.; Wermuth, C. G. *Tetrahedron Lett.* **2001**, *42*, 2115.
13. Draper, T. L.; Bailey, Th. R. *J. Org. Chem.* **1995**, *60*, 748; Estévez, I.; Coelho, A.; Raviña, E. *Synthesis* **1999**, *9*, 1666.
14. Representative procedure for the preparation of compounds **2** and **3** (Scheme 1). A mixture of **1** (1.01 mmol), olefin (1.5 mmol), $Pd(OAc)_2$ (0.10 mmol) and triethylamine (1.52 mmol) in DMF (10 mL) was flushed with argon for 5 min and then deoxygenated and purged. The mixture was stirred and heated under reflux (oil bath 120 °C) under argon until the starting material had been consumed. The reaction mixture was cooled, filtered through a Celite pad and the resulting solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:2).
15. Selected physical and spectral data for compounds **2**. Compound **2**a: Yield: 70%, oil, IR (KBr): 1734; 1664; 1578 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 7.49 (m, 2H, aromatics), 7.44 (m, 3H, aromatics), 7.34 (s, 1H, CH), 4.46 (t, $J = 7.1$ Hz, 2H, CH_2), 4.22 (q, $J = 7.1$ Hz, 2H, CH_2), 2.83 (t, $J = 7.1$ Hz, CH_2), 1.17 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 171.1, 158.7, 146.5, 135.1, 132.9, 130.1, 129.8, 129.5, 128.5, 61.0, 47.7, 33.1, 14.4. HRMS, m/z: calcd for $C_{15}H_{15}BrN_2O_3$ [M^+] 350.0266, found 350.0270.
16. Selected physical and spectral data for compounds **3**. Compound **3a**: Yield: 20%, oil, IR (KBr): 1730; 1721; 1658 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 7.39 (m, 6H, aromatics + CH), 6.41 (d, $J = 15.8$ Hz, 1H, CH), 4.52 (t, $J = 7.1$ Hz, CH_2), 4.24 (q, $J = 7.1$ Hz, 2H, CH_2), 4.12 (q, $J = 7.1$ Hz, 2H, CH_2), 2.87 (t, $J = 7.1$ Hz, 2H, CH_2), 1.29 (t, $J = 7.1$ Hz, 3H, CH_3), 1.19 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 171.3, 165.6, 159.9, 146.2, 139.1, 138.7, 134.6, 129.3, 119.0, 126.6, 125.6, 61.5, 61.0, 47.7, 33.1, 14.5, 142. HRMS, m/z: calcd for $C_{20}H_{22}N_2O_5$ [M^+] 370.1529, found 370.1532.
17. Ismail, M. F.; Shams, N. A.; Rahman, S. E.; Fateen, A. K. *Revue Roumane de Chimie* **1979**, *24*, 899; Sayed, A. A.; Jahine, H.; Zaher, H. A.; Sherif, O. *Indian J. Chem.* **1975**, *4*, 1142.
18. Coelho, A.; Sotelo, E.; Estévez, I.; Raviña, E. *Synthesis* **2001**, *6*, 871876; Coelho, A.; Sotelo, E.; Raviña, E. *Tetrahedron* **2003**, *59*, 2477.
19. Representative procedure for the preparation of compounds **5** and **6** (Scheme 2). A mixture of 4 (1.01 mmol), olefin (2.0 mmol), $Pd(OAc)_2$ (0.10 mmol) and triethyl-

amine (1.52 mmol) in DMF (10 mL) was flushed with argon for 5 min and then deoxygenated and purged. The mixture was stirred and heated under reflux (oil bath 120 °C) under argon until the starting material had been consumed. The reaction mixture was cooled, filtered through a Celite pad and the resulting solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:2).

20. Selected physical and spectral data for compounds **5** and **6**. Compound **5**: Yield: 50%, mp 113–114 °C (dec.), *iso*-PrOH. IR (KBr): 1660; 1586; 1089 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 7.80 (m, 2H, aromatics), 7.70 (d, $J = 9.7$ Hz, 1H, CH), 7.45 (m, 3H, aromatics), 7.04 (d, $J = 9.7$ Hz, 1H, CH), 5.53 (s, 2H, CH_2), 3.52 (s, 2H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 161.3, 145.0, 135.0, 131.3, 131.4, 130.0, 129.3, 126.4, 58.2, 31.3. HRMS, *m/z*: calcd for $C_{12}H_{12}N_2O_2$ [M^+] 216.0899, found 216.0903. Compound **6a**: Yield: 28%, mp 189–190 °C (dec.), *iso*-PrOH. IR (KBr): 1726; 1671; 1546, 1093 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 8.61 (d, $J = 8.2$ Hz, 1H, CH), 8.42 (s, 1H, CH), 8.40 (d, $J = 8.2$ Hz, 1H, CH), 7.58 (m, 5H, aromatics), 5.61 (s, 2H, CH_2), 4.40 (q, $J = 2.4$ Hz, 2H, CH_2), 3.54 (s, 3H, CH_3), 1.39 (t, $J = 2.4$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 165.8, 159.6, 147.5, 135.5, 135.0, 131.9, 131.7, 129.9, 129.8, 129.6, 129.2, 129.1, 128.4, 81.8, 62.3, 14.6. Anal. calcd for $C_{19}H_{18}N_2O_4$ requires C: 67.44; H: 5.36, N: 8.28, Found: C: 67.45; H: 5.39; N: 8.25.
21. Coelho, A.; Sotelo, E.; Novoa, H.; Peeters, M. O.; Blaton, N.; Raviña, E. to be published.
22. Representative procedure for the preparation of compounds **7** (Scheme 3). A mixture of **4** (1.01 mmol), olefin (2.0 mmol), $PdP(o\text{-tolyl}_3)_2Cl_2$ (0.10 mmol) and triethylamine (1.52 mmol) in DMF (10 mL) was flushed with argon for 5 min and then deoxygenated and purged. The mixture was stirred and heated under reflux (oil bath 120 °C) under argon until the starting material had been consumed. The reaction mixture was cooled, filtered through a Celite pad and the resulting solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:2).
23. Selected physical and spectral data for compounds **7**. Compound **7a**: Yield: 70%, mp 146–147 °C (dec.), *iso*-PrOH. IR (KBr): 1719; 1671; 1590 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 7.37 (m, 6H, 5H, aromatics + 1H, CH), 7.12 (s, 1H, CH), 6.42 (d, $J = 15.7$ Hz, 1H, CH), 5.49 (s, 2H, CH_2), 4.22 (q, $J = 7.0$ Hz, 2H, CH_2), 3.50 (s, 3H, CH_3), 1.28 (t, $J = 7.0$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 165.5, 160.6, 146.5, 140.0, 138.9, 134.4, 129.8, 129.4, 129.0, 127.5, 126.2, 81.9, 61.5, 58.3, 14.5. Compound **7b**: Yield: 70%, mp 124–125 °C (dec.), *iso*-PrOH. IR (KBr): 1727; 1670; 1587 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 7.39 (m, 6H, 5H, aromatics + 1H, CH), 7.11 (s, 1H, CH), 6.42 (d, $J = 15.7$ Hz, 1H, CH), 5.48 (s, 2H, CH_2), 3.75 (s, 3H, CH_3), 3.49 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 165.9, 160.5, 146.4, 139.9, 139.1, 134.4, 129.8, 129.3, 129.0, 127.5, 125.7, 125.4, 81.9, 58.3, 52.5.
24. Sotelo, E.; Coelho, A.; Raviña, E. *Tetrahedron Lett.* **2001**, *42*, 8633.
25. Representative procedure for the cleavage of the MOM group in compounds **7**: A mixture of **7** (1.01 mmol), MeOH (5 mL) and 6 N HCl (15 mL) was stirred and heated under reflux (oil bath 120 °C) under argon until the starting material had been consumed. The reaction mixture was cooled and concentrated to dryness under reduced pressure. The resulting residue was poured into water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to give a solid, which was purified by column chromatography (ethyl acetate/hexane 1:2) to afford compounds **8**. Selected physical and spectral data for compounds **8**. Compound **8a**: Yield: 75%, mp 189–190 °C (dec.), *iso*-PrOH. IR (KBr): 2851; 1720; 1669; 1529 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 12.71 (br s, 1H, NH), 7.40 (m, 6H, 5H, aromatics + 1H, CH), 7.17 (s, 1H, CH), 6.45 (d, $J = 15.8$ Hz, 1H, CH), 4.22 (q, $J = 7.1$ Hz, 2H, CH_2), 1.29 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 165.6, 162.5, 147.5, 140.6, 139.3, 134.5, 129.9, 129.3, 129.0, 127.1, 126.3, 61.6, 14.5. Anal. Calcd for $C_{15}H_{14}N_2O_3$ requires C: 66.66; H: 5.22; N: 10.36, found: C: 66.69; H: 5.24; N: 10.40. Compound **8b**: Yield: 78%, mp 203–204 °C (dec.), *iso*-PrOH. IR (KBr): 1724; 1663; 1585 cm^{-1}. ^1H NMR (DMSO-d_6 300 MHz): 12.93 (br s, 1H, NH), 7.41 (m, 6H, 5H, aromatics + 1H, CH), 7.17 (s, 1H, CH), 6.45 (d, $J = 15.9$ Hz, 1H, CH), 3.77 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6 300 MHz): 166.0, 162.1, 147.4, 140.5, 139.5, 134.5, 129.9, 129.3, 129.1, 129.0, 125.7, 52.5. Anal. Calcd for $C_{14}H_{12}N_2O_3$ requires C: 65.62; H: 4.72; N: 10.93, Found: C: 65.70; H: 4.70; N: 10.93.