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Synthesis of α-Acyl-Functionalized Azacycles by Pd-Catalyzed Cross-Coupling Reactions of α-Alkoxyboronates with Lactam-Derived Vinyl Triflates

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Abstract: Alkoxydienyl- and alkoxystyrylboronates were used for Pd-catalyzed cross-coupling reactions with lactam-derived vinyl triflates. The hydrolysis of the coupling products with alkoxystyrylboronates provided the corresponding α-acyl-substituted 3,4-dihydro-(2*H*)-pyridines and 2,3,4,5-tetrahydroazepines in good to high yields. The hydrolysis of the coupling products with alkoxydienylboronates, performed in the presence of Amberlyst 15, resulted in a Nazarov-type cyclization that afforded hexahydro[1]pyrindin-7-ones and 3,4,5,6,7,8-hexahydro-(2*H*)-cyclopenta[*b*]azepin-8-ones. This methodology represents a novel and efficient procedure for the preparation of these classes of azacyclic compounds.

Since it was first reported by Isobe,[1] the Pd-catalyzed functionalization of lactam-derived vinyl triflates[2] and vinyl phosphates[3] has become an important tool for the synthesis of nitrogen-containing heterocycles. We have recently shown that structurally diverse boronic acids and esters efficiently couple with vinyl triflates derived from six- and seven-membered *N*-alkoxycarbonyl lactams to give the corresponding 6- and 7-subsituted 3,4-dihydro-(*2H*)-pyridines and 2,3,4,5-tetrahydroazepines.[4] Using this methodology we were able to introduce alkyl, alkenyl, allyl, aryl, and heteroaryl groups. To functionalize those heterocycles with various acyl groups,[5] we decided to exploit a new class of readily accessible alkoxyboronates[6] which appeared suitable for transferring masked acyl moieties by a Suzuki−Miyaura cross-coupling reaction. Subsequent hydrolysis would then furnish the corresponding 6-acyl-3,4-dihydro-(2*H*)-pyridines and 7-acyl-2,3,4,5-tetrahydroazepines. Alkoxystannanes have indeed been employed for this reason but their use has been limited to one example only.[2b] In any case the use of boronates, where possible, is preferable because of their low toxicity and environmental impact.

We have coupled two different classes of alkoxyboronates with *N*-alkoxycarbonyl triflates **1a**,**b** and **10** (Schemes 1 and 3). Alkoxydienylboronates **2** and **3** allow the incorporation of α,*β*-unsaturated acyl moieties, and alkoxystyrylboronates **14** and **15** permit the introduction of aryl-substituted α-acyl groups. These alkoxyboronates were prepared in high yields according to the reported procedure.[6] As for the triflates, besides the *N*-Cbz protection utilized in **1a** and **10**, we also employed the *N*-methoxycarbonyl group (in **1b**)[7] to have an alternative protecting group for synthetic purposes. Moreover it should guarantee a higher stability in the presence of acids than the *N*-Boc protection, which we have employed in our previous studies.[4a,b]

The reaction between **1a** and boronate **2** was carried out in THF at 50 °C, in the presence of 5% $(Ph_3P)_2PdCl_2$ as a catalyst and aqueous 2 M Na_2CO_3 as a base (Scheme 1). It was complete after 3 h, affording ethoxybutadienyl tetrahydropyridine **4** in 77% yield after chromatographic purification. Coupling of **1a** with the methyl-substituted ethoxydienylboronate **3** furnished, under the same conditions, product **5** in 78% yield.

Hydrolysis of **4** was first carried out by dissolving the starting material in $CHCl_3$ in the presence of the acidic Amberlyst 15 resin at room temperature.[8] After 2.5 h the TLC showed the complete conversion of **4** into a more polar product that was purified and fully characterized: to our surprise its structure corresponded to that of hexahydro[1]pyrindin-7-one compound **8** (obtained in 73% yield after chromatography).[9] An analogous result

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(1) (a) Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737−3744. (b) Okita, T.; Isobe, M. *Synlett* **1994**, 589−590.

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(5) Pd-catalyzed carbonylation of lactam-derived triflates might represent a general route (yet to be explored) for the incorporation of an acyl moiety. So far, Pd-catalyzed carbonylation has been applied to these systems only for the introduction of ester and amide groups (see ref 2b and references therein).

(6) Balma Tivola, P.; Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett*. **2002**, *4*, 1275−1277.

(7) Compound **1b** was prepared in 89% yield from the corresponding *N*-CO_2Me protected *δ*-valerolactam according to the procedure reported for **1a** in ref 4a. ^{1}H NMR ($CDCl_3$) *δ* 5.30 (t, *J* = 3.5 Hz, 1 H), 3.78 (s, 3 H), 3.65 (m, 2 H), 2.26 (m, 2 H), 1.78 (m, 2 H).

(8) Prandi, C.; Venturello, P. *J. Org. Chem*. **1994**, *59*, 5458−5462.

(9) The structure of this compound was easily assigned by ^{1}H and ^{13}C NMR analysis: in the proton spectrum, the protons on C6 form an AX system with geminal coupling *J* = 15.8 Hz. Only one of the two protons couples significantly with 5-H (*J* = 6.6 Hz). The methyl group at position 5 resonates as a doublet (*J* = 7.0 Hz) due to the coupling with 5-H. In the carbon spectrum, a triplet at 42.8 ppm and a doublet at 33.4 are attributable to C6 and C5, respectively.

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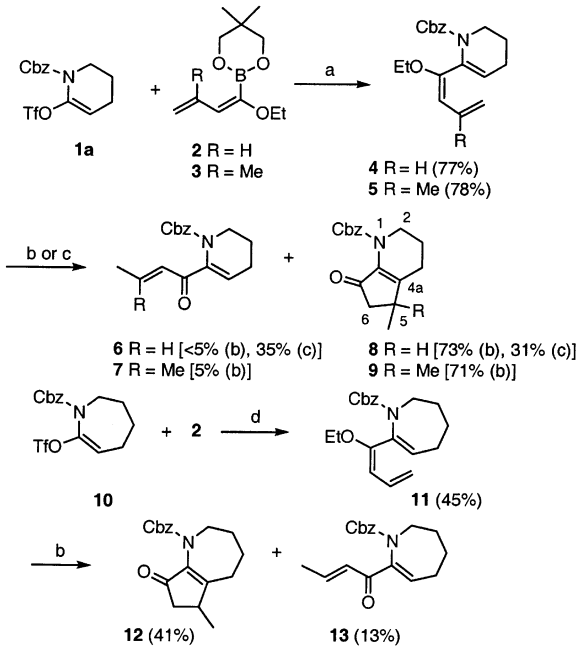
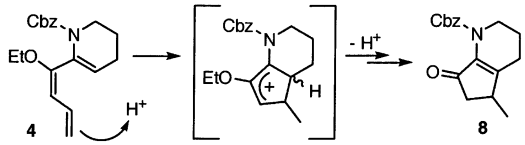
SCHEME 1[a]



[a] Conditions: (a) $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M Na_2CO_3, 50 °C; (b) Amberlyst 15, $CHCl_3$, 25 °C; (c) 0.02 M HCl, MeOH, 25 °C; (d) $(Ph_3P)_4Pd$ (3%), toluene, EtOH, 2 M K_2CO_3, 25 °C.

SCHEME 2



was obtained when **5** was subjected to the same conditions, affording pure **9** in 71% yield after chromatography. In this case a very small amount (about 5% yield) of α,β-unsaturated ketone **7** was obtained from the chromatography of the crude reaction mixture.

α,β-Unsaturated ketone **6** was isolated from a mixture containing product **8** when the hydrolysis of **4** was carried out under aqueous acidic conditions, i.e., dissolving **4** in a dilute HCl solution in MeOH and stirring at room temperature. After 2 h the reaction was complete (by TLC) and ^{1}H NMR analysis of the crude reaction mixture revealed the presence of two major products in a 1:1 ratio. After chromatographic separation, **6** and **8** were obtained in moderate yields (35 and 31%, respectively).

The formation of product **8** (and **9**) can be accounted for by the initial protonation of the distal double bond[10] followed by an immediate Nazarov-type electrocyclization (Scheme 2). The Nazarov cyclization[11] usually occurs under quite drastic conditions (concentrated protic acids and high temperature)[12] unless either Lewis acids in aprotic media or β-silyl- or β-stannyl-substituted dienones are used to perform the reaction.[13,14] In our case the reaction proceeds smoothly at room temperature presumably due to the facile loss of the bridgehead proton from the intermediate cation.[11c] Although unsaturated ketone **6** could be invoked as an intermediate in a Nazarov-type process leading to **8**, when pure **6** was dissolved in $CHCl_3$ with Amberlyst 15 it did not give rise to **8**. Our mild procedure to form compounds **8** and **9**, which formally derive from the Nazarov cyclization of α,β-unsaturated dienones **6** and **7**, could therefore be conveniently used for the preparation of compounds containing the hexahydro[1]pyrindin-7-one structure, a useful intermediate in natural product synthesis.[15] The above synthetic sequence was also applied to the synthesis of the larger 3,4,5,6,7,8-hexahydro-(2*H*)-cyclopenta[*b*]azepin-8-one **12** (Scheme 1). Coupling of caprolactam-derived vinyl triflate **10**[4a] with **2** (Scheme 1) afforded azepine derivative **11** in 45% yield after chromatography. As already observed for this triflate,[4a] the coupling yield was lower compared to that obtained with the corresponding six-membered triflate **1a** due to its partial decomposition during the course of the reaction. Subsequent hydrolysis over Amberlyst 15 gave the Nazarov product **12** in 41% yield after chromatography together with a smaller amount of α,β-unsaturated ketone **13** (13%).

The incorporation of aryl-substituted α-acyl moieties was realized by coupling the suitable alkoxystyrylboronates **14** and **15** with triflates **1a**,**b** and **10** (Scheme 3). The reaction between **1a** and **14**, carried out in THF in the presence of 5% $(Ph_3P)_2PdCl_2$ and 2 M Na_2CO_3, smoothly gave product **16** in 81% yield after 3 h at 50 °C. When 2-methyl-substituted styryl boronate **15** was used as the coupling partner with **1a** and **1b**, the reaction rate apparently decreased dramatically, the conversions to **17** and **18** being about 5 and 30%, respectively, after 4 h at 60 °C. The increased steric hindrance due to the further degree of substitution at the C−C double bond in **15** could be a reason for the low conversion observed.[16] The coupling yields were greatly improved when the reactions between **15** and triflates **1a** and **1b** were conducted in toluene in the presence of $(Ph_3P)_4Pd$ (3%) as a catalyst, aqueous 2 M K_2CO_3, and with EtOH as a cosolvent. GC monitoring revealed the disappearance of the reagents after 4 h at room temperature in the case of triflate **1b**. The reaction of *N*-Cbz-protected triflate **1a** was slower, being complete after 16 h at 25 °C and 2 h

(10) The initial double bond protonation that takes place in the formation of **8** is consistent with the proposed mechanism of γ-pyranone ring closure observed when substrates containing the same alkoxydienyl moiety were hydrolyzed. Prandi, C.; Venturello, P. *J. Org. Chem.* **1994**, *54*, 3494−3496.

(11) (a) Nazarov, I. N.; Torgov, I. B.; Terekhova, L. N. *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* **1942**, 200. (b) Braude, E. A.; Forbes, W. F. *J. Chem. Soc.* **1953**, 2208−2216. (c) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221−10228 and references therein.

(12) For example, the cyclization of 2-(3-methylbut-2-enoyl)indoles to give the corresponding cyclopenta[*b*]indolones occurred by heating at 110 °C with polyphosphoric acid: Bergman, J.; Venemalm, L.; Gogoll, A. *Tetrahedron* **1990**, *46*, 6067−6084.

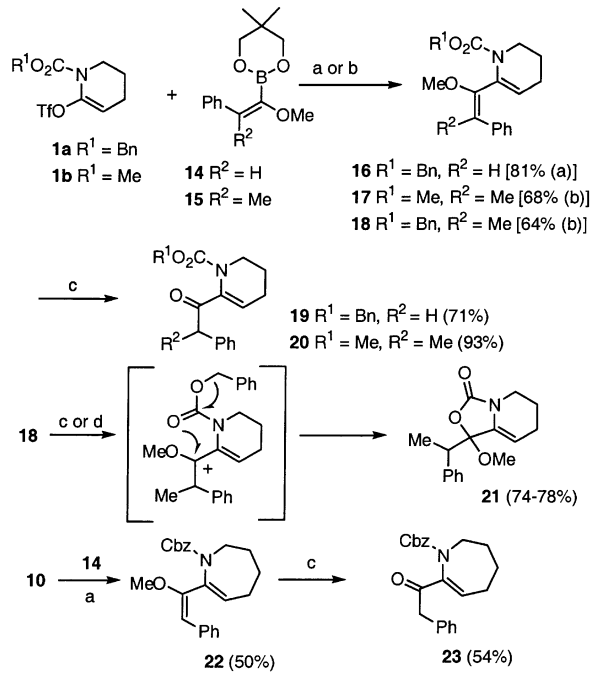
(13) (a) Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *J. Org. Chem.* **1980**, *45*, 1046−1045. (b) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017−3028. (c) Jones, T. K.; Denmark, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 2642−2645. (b) Peel, M. R.; Johnson, C. R. *Tetrahedron Lett.* **1986**, *27*, 5947−5950.

(14) The Nazarov reaction carried out on compounds closely related to those reported in ref 12 occurred after heating for 2 h in the presence of BF_3: Miki, Y.; Hachiken, H.; Sugimoto, Y.; Yanase, N. *Heterocycles* **1997**, *45*, 1759−1766.

(15) For example see: Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798−811.

(16) Progressive degradation of boronate **15** during the course of the reaction also has been observed. We isolated by chromatography a product having the following structure: Ph(Me)C═C(OMe)H. In the ^{1}H NMR spectrum of the reaction mixtures, the ═CH signal at 6.38 ppm of this olefin was diagnostic.

SCHEME 3[a]



[a] Conditions: (a) $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M Na_2CO_3, 50 °C; (b) $(Ph_3P)_4Pd$ (3%), toluene, EtOH, 2 M K_2CO_3, 25 °C; (c) Amberlyst 15, $CHCl_3$, 25 °C; (d) 0.5 M HCl, MeOH, 25 °C, 16 h.

at 40 °C. Chromatographic purifications afforded **17** and **18** in 68% and 64% yield, respectively.

The hydrolysis of **16** in the presence of Amberlyst 15 in $CHCl_3$ was quite slow compared with that of **4** and **5**, but provided the corresponding α-aryl ketone **19** in 71% yield after 8 h at room temperature. The *N*-CO_2Me protection in compound **17** was stable under the same hydrolysis conditions since compound **20** was obtained in 93% yield after 12 h at room temperature.

When the same reaction was performed on *N*-Cbz-protected compound **18**, oxazolidinone **21** was obtained as the only product after 20 h at room temperature (74% yield after chromatography). The formation of **21** can be explained, as depicted in Scheme 3, by attack of the carbamate C═O group on the carbocation formed after initial protonation of the double bond. The process is favored by the loss of the benzyl cation.[17,18] Hydrolysis of **18** in a diluted methanolic HCl solution confirmed this experimental result, since it afforded **21** as the only detectable product (78% after chromatography).[19,20] Synthetically, therefore, the use of the *N*-CO_2Me group is preferable to *N*-Cbz protection in our methodology since the formation of a methyl cation through the mechanism reported in Scheme 3 is disfavored. Finally, coupling of caprolactam-derived vinyl triflate **10** with **14** (Scheme 3) gave **22** in inferior yield (50%) than the coupling of **14** with **1a**. Hydrolysis under the usual conditions afforded α-acyl azepine **23** in 54% yield.

In conclusion we have successfully used alkoxydienyl- and alkoxystyrylboronates for Pd-catalyzed cross-coupling reactions with lactam-derived vinyl triflates. The hydrolysis of the coupling products with alkoxystyrylboronates provided the corresponding α-acyl-substituted 3,4-dihydro-(2*H*)-pyridines and 2,3,4,5-tetrahydroazepines in good to high yields. The hydrolysis of the coupling products with alkoxydienylboronates, performed with Amberlyst 15, resulted instead in a Nazarov-type cyclization that afforded hexahydro[1]pyrindin-7-ones and 3,4,5,6,7,8-hexahydro-(2*H*)-cyclopenta[*b*]azepin-8-ones. This methodology represents a novel and efficient procedure for the preparation of these classes of azacyclic compounds. The extension of the methodology to the synthesis of more complex heterocyclic structures is currently under study.

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Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In the hydrolysis of **16**, about 10% of the crude reaction mixture (from ^{1}H NMR analysis) was attributable to the corresponding cyclic carbamate, but this was not isolated.

(18) In the ^{1}H NMR spectrum of **21** the proton on C5 resonates at 4.83 ppm (shielded due to the lack of conjugation with the C═O) and the *O*Me group resonates at 3.25 ppm as a singlet. In the ^{13}C NMR spectrum, C5 resonates at 98.0 ppm (usually at about 120 ppm in compounds such as **19** and **20**) and the *O*Me as a quartet at 48.2 ppm. The quaternary acetal C atom resonates at 108.6 ppm as a singlet and the C═O group at 153.6 ppm. In the IR spectrum this has a strong absorption at 1759 cm^{-1}.

(19) Product **21** was also recovered during an attempt at purification of compound **18** on silica gel without the addition of Et_3N to the eluant.

(20) A similar process has been reported very recently by Comins, although in that case the cyclization, which took place after addition of I_2 to a double bond, gave rise to a six-membered cyclic carbamate: Williams, A. L.; Grillo, T. A.; Comins, D. L. *J. Org. Chem.* **2002**, *67*, 1972−1973.