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Substituted oxazolo[4,5-*b*]pyridin-2(3*H*)-ones : Functionalization at 6-position.

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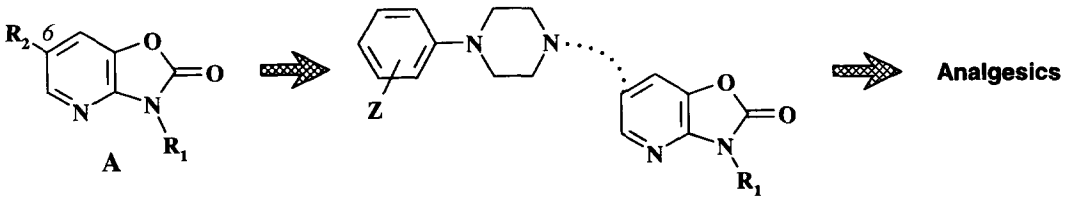
Abstract : Substituted oxazolo[4,5-*b*]pyridin-2(3*H*)-ones were obtained by functionalization at 6-position with various substituents (alkyl, aryl, carbonyl chains,...) *via* reactions catalyzed with palladium.

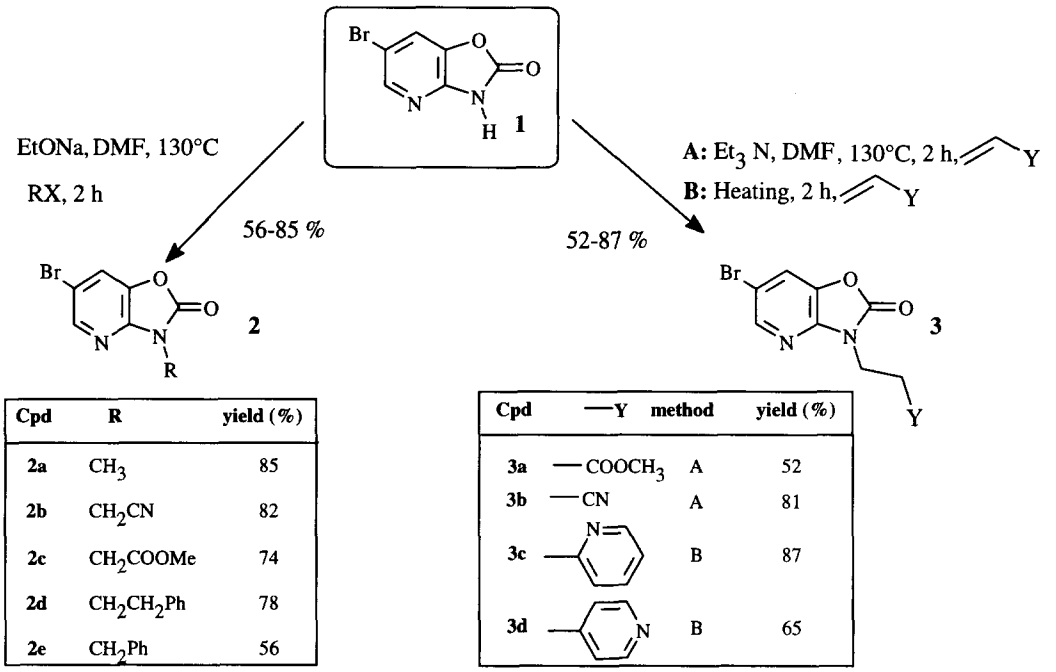
The two main groups of analgesics on the market are the opioids such as morphine, codeine, dextropropoxyphen, and the cyclooxygenase inhibitors (nonsteroidal antiinflammatory agents, NSAI) including aspirin, ibuprofen, indomethacin and paracetamol.[1] However, each class has its drawbacks : cyclooxygenase inhibitors induce gastrointestinal lesions while opioates induce tolerance, constipation, respiratory depression, physical dependency and fear of addiction. The main objective in current pain research is to develop now, improved non-opioid analgesics which are as effective as the opioids but without their side effects.[2-3]

In connection with our studies on polyheterocyclic compounds with potential biological activity,[4] we had synthetized substituted oxazolo[4,5-*b*]pyridin-2(3*H*)-ones having the general formula **A** functionalized at 6-position which are good intermediates in our research project. Indeed, these derivatives after modifications then introduction of aryl piperazine unit may afford potential analgesics.



Compound **1** was easily obtained directly by bromination of oxazolo[4,5-*b*]pyridin-2(3*H*)-one in very good yield.[5] Then **1** was transformed to compounds **2** and **3** by regioselective *N*-exocyclic substitution of oxazolo system as well by *N*-alkylation with halogeno derivatives as by Michael condensation with the appropriate olefins. Compounds **2** were obtained in DMF using sodium ethylate as base.[6] Two methods were employed for the synthesis of **3** using either triethylamine in DMF at 130°C (method A) or by heating with the 2- or 4-vinylpyridine used as reagent and as solvent (method B) (Scheme 1).[7]

Scheme 1

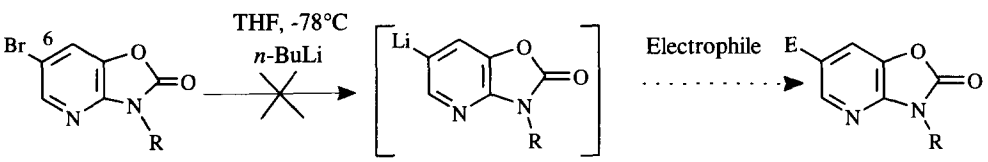


Cpd	R	yield (%)
2a	CH_3	85
2b	CH_2CN	82
2c	CH_2COOMe	74
2d	CH_2CH_2Ph	78
2e	CH_2Ph	56

Cpd	—Y	method	yield (%)
3a	—$COOCH_3$	A	52
3b	—CN	A	81
3c		B	87
3d		B	65

First the functionalization at 6-position had been tried *via* anionic reaction using *n*-butyllithium at -78 °C (Scheme 2). In fact this methodology led to a rapid degradation of the substrat, and was abandonned. Consequently we have applied the Heck, Suzuki and Stille methologies to supply our problems.

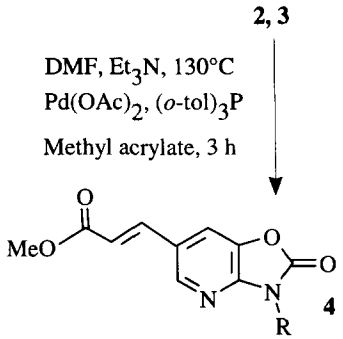
Scheme 2



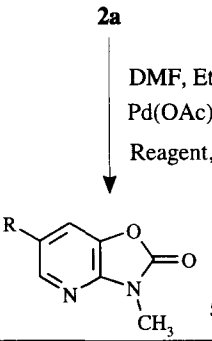
The Heck reaction has shown great versatility in the construction of carbon-aryl bond.[8] Although generally utilized in the formation of cyclic or linear carbon-based systems, the Heck reaction has been efficiently applied to heterocyclic ring systems.[9]

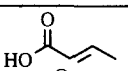
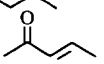
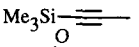
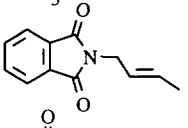
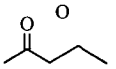
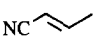
Syntheses of compounds **4** and **5** were performed in good yields (Scheme 3) according to Heck methodology using palladium (II) acetate and tri-*o*-tolylphosphine in DMF with triethylamine as base.[10]

Scheme 3



Cpd	R	yield (%)
4a	CH_3	65
4b	CH_2CN	65
4c	CH_2COOCH_3	79
4d	CH_2Ph	52
4e	$(CH_2)_2Ph$	72
4f	$(CH_2)_2COOCH_3$	70
4g	$(CH_2)_2CN$	73
4h	$(CH_2)_2$ 	84
4i	$(CH_2)_2$ 	75

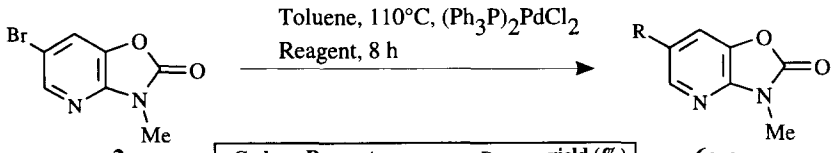


Cpd	Reagent	R—	yield (%)
5a	acrylic acid		70[a]
5b	butyl vinyl ether[b]		90
5c	ethyl 1-propenyl ether[b]		40
5d	3-buten-2-one		85
5e	trimethylsilylacetylene		92
5f	N-allylphtalimide		69
5g	3-buten-2-ol		73
5h	acrylonitrile		65

a) isolated under ester form **4a** b) then HCl 10%

Compounds **6** were prepared according to Stille's reaction by using for the key reaction dichlorobis(triphenylphosphine)palladium (II) and commercially tetraalkyltin reagent (methyl, butyl and vinyl) in toluene (Scheme 4) .[11]

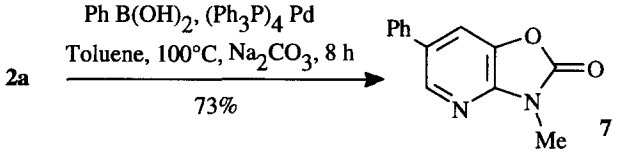
Scheme 4



Cpd	Reagent	R	yield (%)
6a	tetramethyltin	CH_3	72
6b	tetrabutyltin	CH_2=CH	62
6c	tributylvinyltin	CH_3-$(CH_2)_3$	86

We chose also to investigate the palladium catalyzed cross coupling of 6-bromo-oxazolo[4,5-*b*]pyridin-2(3*H*)-ones (**1**) with the commercially available phenylboronic acid using Suzuki methodology.[12] Compound **7** was obtained by this way in 73% yield (Scheme 5).

Scheme 5



Using commercially or easily available reagents and catalysts, Heck or Stille or Suzuki reaction have shown to be an efficient method for generating substituted oxazolo[4,5-*b*]pyridine-2(3*H*)-ones at position 6. This methodologies should prove to be useful in the synthesis of functionalized bicyclic heterocycles. The successful application of this chemistry for preparation of pharmaceutical agents will be disclosed in the future.

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References and Notes

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6. **3-Methyl-6-bromooxazolo[4,5-*b*]pyridin-2(3*H*)-one 2a** :To a solution of sodium ethylate freshly prepared (4.8 mg of sodium in 6 ml of ethanol) was slowly added compound **1** (0.430 g, 2 mmol). The mixture was stirred 1 hour at room temperature, then ethanol was evaporated. To the resulting mixture in DMF (6 ml) was added dropwise a solution of methyl iodide (0.426 mg, 3 mmol) in DMF (0.5 ml). The mixture was refluxed two hours, then after cooling, evaporation of the solvent under reduce pressure, the residue was treated with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was chromatographied on a silica gel column with CH_2Cl_2 as eluent to give compound **2a** (391 mg, 85%). m.p. 125-127°C. IR (KBr): 1770 cm^{-1}. ^{1}H-NMR (300MHz; $CDCl_3$), δ 3.47(3H, s, CH_3),7.52 (1H, s, J=2.2Hz, H-7), 8.16 (1H, s, J=2.2Hz, H-5).
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10. **General procedure for compounds 4a-i** :To stirred solution of 6-bromo-*N*-substituted-oxazolo[4,5-*b*]pyridin-2(3*H*)-ones **2** or **3** (2.18 mmol) in *N,N*-dimethylformamide (15 ml) was successively added methyl acrylate (0.23 ml, 2.62 mmol), triethylamine (0.36 ml, 2.62 mmol), palladium diacetate (5 mg, 0.02 mml) and tri-*o*-tolylphosphine (26 mg, 0.08 mmol). The mixture was stirred at 130 °C under argon during 3 hours. After cooling, the residue obtained after concentration under *vacuum* was hydrolyzed and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography on a silical gel column with CH_2Cl_2 as eluent to give the desired compounds. **(*E*)-3-(3-Methyl-2-oxo-4,3- dihydrooxazolo[4,5-*b*]pyridin-6-yl)acrylic acid methyl ester 4a** :Yield: 65%. m.p. 212-214°C. IR (KBr): 1770, 1680 cm^{-1}. MS *m/z*: 235 (M+1). ^{1}H-NMR (300MHz; $CDCl_3$), δ 3.50 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 6.40 (1H, d, J=16.2Hz, =CH), 7.57 (1H, d, J=1.5Hz, H-7), 7.69 (1H, d, J=16.2Hz, =CH), 8.23 (1H, d, J=1.5Hz, H-5).
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