



## Ecolec's Technical Bulletin 1

Newly available a set of 12 highly versatile acyliminium precursors

Ecolec is a Belgian enterprise dedicated to the development of electro-organic synthesis routes towards a vast array of fine chemicals. It grew out of research done in the late seventies and early eighties at the Ghent University and later from 2003-2009 at Peptisyntha's (Solvay-B) research labs.

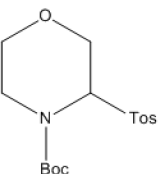
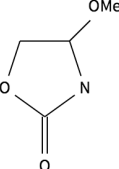
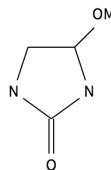
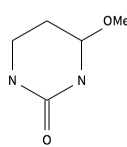
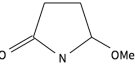
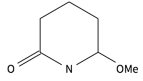
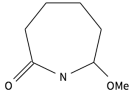
### Introduction:

It is generally recognized that electro-organic chemistry, especially the anodic oxidation of nitrogen containing compounds, offers environmentally clean routes towards highly versatile intermediates often inaccessible via other chemistries. In spite of this we are not aware of any industrial development in this field, (although big chemical companies like Hoechst and BASF once held some patents) nor do the retail companies offer any of these intermediates in their catalogues thereby not really encouraging research people to consider such intermediates in designing synthetic strategies toward their end products.

We at Ecolec try to remedy this by offering a first set of those intermediates whose synthesis has been conducted on large scale (most often >1kg a few at >25kg) and thereby assuring the supply chain, should any of these intermediates become candidates for scale up.

### List of products:

Cat n°	Name	Structure	Cas n°	Price 10g/25g
E10620	N-Formyl-2OMe-Pyrrolidine		61020-06-2	200€ / 375€
E10610	N-Formyl-2OMe-Piperidine		61020-07-3	200€ / 375€
E10605	N-Formyl-3OMe-Morpholine		61020-09-5	200€ / 375€
E10621	N-Boc-2TosylPyrrolidine		NC*	400€ / 750€
E10611	N-Boc-2TosylPiperidine		NC*	400€ / 750€

E10606	N-Boc-2TosylMorpholine		NC*	400€ / 750€
E10655	4OMe-oxazolidin-2-on		14441-94-2	400€ / 750€
E10625	4OMe-imidazolidin-2-on		94471-24-6	400€ / 750€
E10630	4OMe-tetrahydropyrronidin-2-on		1244855-97-5	400€ / 750€
E10645	5OMe-butyrolactam		63853-74-7	400€ / 750€
E10650	6OMe-valerolactam		63853-82-7	400€ / 750€
E10651	7OMe-caprolactam		63853-81-6	400€ / 750€

\*NC = New Compound

### Historical background:

Already in 1964 Ross and Finkelstein (1) reported about the anodic oxidation of dimethylformamide leading to the methoxylated derivative, but it was only after the labs of Nyberg and Ebersson in Lund (2) and of Shono (3) in Kyoto in the late seventies and early eighties reported their results that this research field really took off. We have been one of the earlier followers of the Ebersson approach building our own capillary gap cell (4) allowing the synthesis of >> 100mmoles at lab scale.

Later on this research field was further widened by Steckhan in Bonn (5) Seebach in Zürich (6) Dhimane in Paris (7) and Moeller in St-Louis (8) who all demonstrated that with the synthesis of ECO derived chiral synthons, many alkaloids and peptidomimetics became easily accessible via this routes.

The most exhaustive review written by Steckhan describing all these possibilities has been edited post-mortem in the Chapter 15 VIII p.570-588 of Organic Electrochemistry Marcel Dekker Inc. 2001 (Ed. Lund and Hammerich).

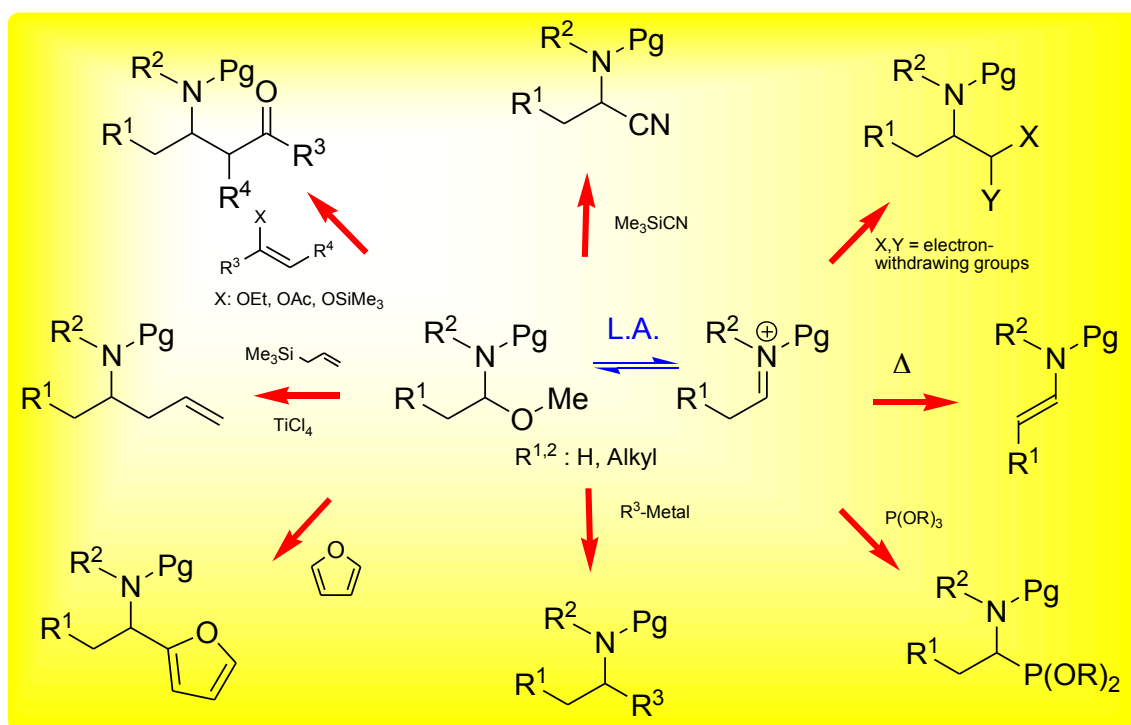
### Approaches towards N-protected alfa substituted compounds and their applications:

There exist two approaches; either the direct functionalization (hydroxylation, alkoxylation or acyloxylation) of N-protected amines or the decarboxylative (mainly) methoxylation of protected amino acids (the so called Hofer Moest variant as first practised by the Tanabe researchers (9)).

We have experience with both and clearly the second one is less stringent with regard to the corrosive nature of the reaction conditions and the ease of work-up. Unfortunately this remains limited to the use of protected amino acids and aminomalonates. As one speaks of protected amino compounds this can take many forms: acyl, urethane, tosyl and phosphono protective groups are all compatible. Most importantly cyclic amides like lactams, cyclic urethanes like oxazolidinones or even imidazolidones are equally susceptible towards anodic oxidation.

### Applications:

With regard to applications the whole realm of acyliminium chemistry is opened up (cfr. reaction scheme 1). We have a lot of experience in this field and are willing to guide the interested customer.



Reaction Scheme 1

Of the many possible applications we can sum up the cyanation (we were the very first to report the Lewis acid catalyzed reaction of alpha methoxy amides with TMSCN; ref. 4) the allylation, the Grignard and Cu derived organometallic reactions, the silylenol ether and the dicarbonyl condensation (including malonates), the phosphonation, the elimination toward enamides, the amidoalkylation of aromatic compounds, but also internal cyclization reactions are possible.

### Our first portfolio of compounds:

A first attempt at commercialization was initiated by Wistrand who wrote an article in Janssen Chimica Acta (10) at the same time offering the methoxylated N-formyl piperidine and morpholine in the catalog. This very limited offer did not appeal to the scientific community. We come up with a far larger portfolio at affordable prices and realistic perspectives in view of industrial applications. The same two compounds together with the formylated pyrrolidine as synthetic grades (95%+), which is usually sufficient for further applications.

The same Boc protected derivatives which are more difficult to purify we offer in the form of their  $\alpha$ -sulphones counterparts which are stable, pure and crystalline derivatives with equal, if not better, applicability (for a review on the chemistry of such kind of intermediates cfr. 11).

The last six methoxylated cyclic compounds which are all crystalline products of high purity have also found many applications.

If a compound of similar nature is not taken up in the list interests you please feel free to contact us.

1. Ross et al. JACS (1964) 86 p;2745
2. Cedheim et al Act Chem Scan (1975) B29 617
3. Shono et al. JACS (1975) 97 4264 // Shono Top Curr Chem (1988) 148 p131
4. Asher et al. Tetrah Lett (1981) 22 141 // Duquet et al Bull Chem Soc Belg (1985) 94 ( ?)
5. Brungs et al. Journ Chim Phys (1996) 93 575 // Kardassis et al (1998) 54 3471 and 3478
6. Seebach et al. Helv Chim Acta (1989) 72 401 // Renaud et al Helv Chim Acta (1986) 69 1704
7. David et al Synlett (2004) 6 1029 // Le Corre et al Tetrah Lett (2005) 46 7495
8. Moeller Tetrah (2000) 56 9527 // Beal et al Tetrah (2000) 56 10113
9. Iwasaki et al. Journ Org Chem (1977) 42 2419
10. Wistran Janssen Chim Acta (1986) 4 34
11. Petrini Chem Rev (2005) 105 3949