Aza-Achmatowicz route to novel cyanocarbacephems

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Novel carbacephems are prepared through aza-Achmatowicz rearrangement of 4-(2-furyl)azetidinones.

Beta lactam antibiotics occupy a privileged position in organic chemistry, because of their clinical importance and the interesting chemical problems that they present.[1] Unfortunately, widespread use of these antibiotics during the past decades has caused several pathogens to develop resistance.[2] This has engendered considerable medicinal chemistry activity directed toward the development of viable new types of β-lactams.[3]

Carbacephems,[4] exemplified by Loracarbef **5**,[5] are a promising new family of such antibiotics. New synthetic opportunities in the carbacephem area are available through the aza-Achmatowicz rearrangement, defined as the conversion of furylamides **1** to heterocycles **2** (Fig. 1).[6] Chirality at the furylic site in **1** is conserved during this reaction.[7] Groups R^1 and R^2 in **1** may be independent or joined into a ring; therefore β-lactam **3** might result if R^1 and R^2 were an azetidinone unit. Compound **3** could serve as the progenitor of novel carbacephems **4**, wherein diverse groups 'G', which might well fine-tune bioactivity, could be introduced thanks to the ketone present in **3**. These hypotheses have been reduced to practice as described herein.‡

Appropriate azetidinones of either *cis* or *trans* stereochemistry (Scheme 1)§ were obtained by literature methods.[8] The *para*-anisyl ('PAN') N-blocking group was oxidatively removed[9] at the stage of **7** and **11**, to yield the actual aza-Achmatowicz substrates **8** and **12**.

Cis compound **8** was readily advanced to **15**, rearrangement of which to carbacepham building block **16** was best effected with CF_3CO_2H in $CHCl_3$ (Scheme 2). Intermediate **16** differs from carbacephams by having a MeO at a site where a C_1 unit is required. It was hoped that introduction of the requisite functionality could be achieved through reaction of enamide **19** with cyanogen halides.[10] Therefore, heterocycle **16** was converted into acetate **18**, which formed *cis* enamide **19** upon reaction with pyridinium toluene-*p*-sulfonate (PPTS)[11] in refluxing benzene. In a like fashion, and in identical yields, *trans* enamide **20** was obtained from **12**, except that a methyl (Mec, **20**), instead of isobutyl (Ibc, **16**) carbamate was installed as the side-chain blocking group.¶

Both enamides were inert to cyanogen halides, but instead formed a stable, crystalline dichloride **25** (Fig. 2) upon reaction with Cl_2 (0 °C, CH_2Cl_2, 98%). Reaction of **25** with cyanide ion

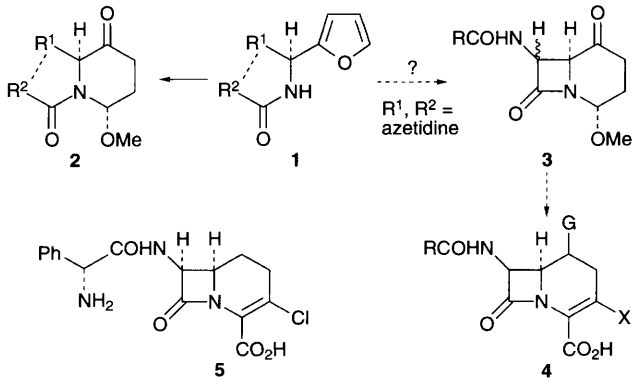
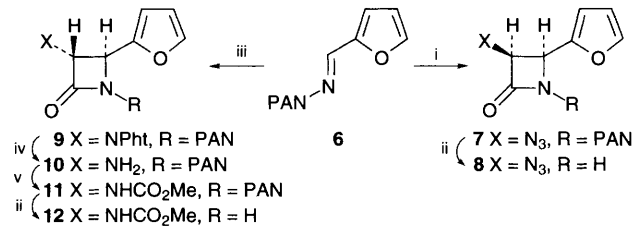
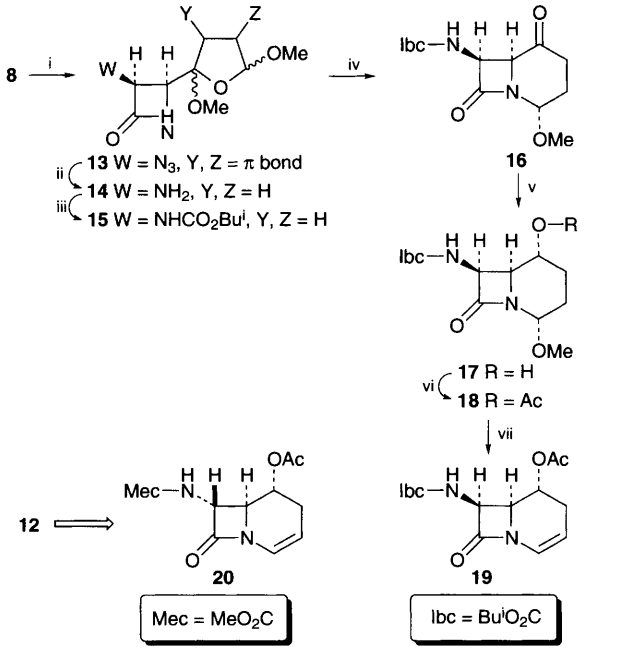


Fig. 1



Scheme 1 *Reagents and conditions*: i, $N_3CH_2CO_2H$, TFA, Et_3N, THF, 0 °C, 93%; ii, CAN, MeOH, 0 °C, 58%; iii, $PhtNCH_2COCl$, Et_3N, 98%; iv, $N_2H_4{\cdot}H_2O$, MeOH, 95%; v, MeO_2CCl, sat. aq. $NaHCO_3$, 0 °C, 98% (Pht = phthaloyl)



Scheme 2 *Reagents and conditions*: i, Br_2, MeOH, −20 °C, then NH_3, 95%; ii, H_2, Ra-Ni, 1500 psi, 50 °C, 100%; iii, Bu^iO_2CCl, sat. $NaHCO_3$, 0 °C, 85%; iv, 10% TFA–$CHCl_3$, 0 °C, 99%; v, $NaBH_4$, EtOH, −60 °C, 95%; vi, Ac_2O, pyridine, 92%; vii, PPTS, benzene reflux, 86%

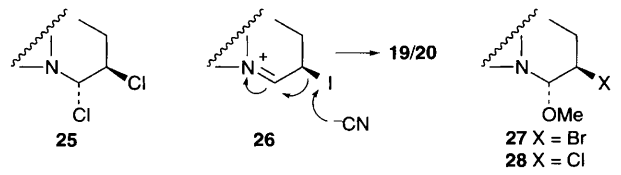
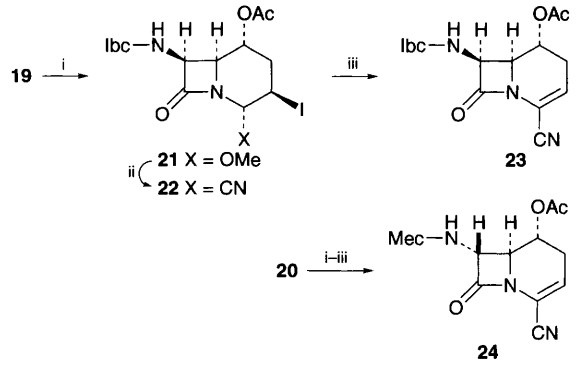


Fig. 2



Scheme 3 *Reagents and conditions*: i, I_2, MeOH, solid $NaHCO_3$, 0 °C, 91% *cis* series, 86% *trans* series; ii, TMSCN (15 equiv.), $BF_3{\cdot}OEt_2$ (2 equiv.), CH_2Cl_2, room temp., 63% *cis* or *trans* series (see text); iii, Et_3N, CH_2Cl_2, room temperature, 98% *cis* or *trans* series

was anticipated to proceed with displacement of the more mobile of the two halogens. However, delivery of various forms of ^-CN** to **25** yielded complex mixtures.

By contrast, the enamides reacted with I_2 in MeOH–$NaHCO_3$ to furnish *trans* diaxial methoxy iodides in excellent yield (*e.g.* **21**, Scheme 3). Treatment of these intermediates with trimethylsilyl cyanide (TMSCN) and $BF_3{\cdot}OEt_2$ induced Anteunis-type cyanation,[12] thus achieving the desired introduction of a C_1 group. It is noteworthy that the β-lactam withstood this transformation unscathed. Finally, HI elimination occurred cleanly upon exposure of the iodonitriles to Et_3N, providing the novel cyanocarbacephems **23** and **24**.

Interestingly, cyanation of the methoxy iodides reproducibly furnished a 2.5 : 1 mixture of readily separable, desired nitrile (62–65%) and starting enamide (24–30%). The latter probably forms through deiodination of acyliminium ion **26** by ^-CN, with consequent formation of ICN. It should also be noted that methanolic pyridinium tribromide (−78 °C, 85%) or *N*-chlorosuccinimide (−20 °C, 89%) converted either enamide into methoxy halides **27** and **28**, respectively. Bromides did react in the Anteunis cyanation, but slowly and not very cleanly, while the chlorides were essentially inert. The behaviour **27** and **28** is apparently due to increasing inductive destabilization of an acyliminium ion intermediate of the type **26** by progressively more electronegative neighbouring halogen atoms.

In summary, carbacephems are now within the scope of aza-Achmatowicz transformations. We are hopeful that the chemistry described herein will provide an incentive for the pharmacological exploration of the newly available cyanocarbacephems.

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Footnotes

† Fellow of the Alfred P. Sloan Foundation, 1994–1996.

‡ All compounds described herein were fully characterized by ^1H and ^{13}C NMR, IR, low and high resolution mass spectroscopy. All yields refer to chromatographed, pure (NMR, TLC) compounds.

§ All compounds described here are racemic. However, technology for enantiocontrolled ketene–imine condensation is known (ref. 1) and therefore translation of these results to the scalemic series should be possible.

¶ An isobutyl carbamate alleviated severe problems with the insolubility of *cis* β-lactams in ordinary organic solvents. A methyl carbamate (Mec in **21**) constituted an adequate level of protection for the much more soluble trans compounds.

** Li^+, Na^+, K^+, or Bu_4N^+ cyanide, in anhydrous or aqueous DMF, DMSO or EtOH.

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