Azoacetates as Synthons for the Azetidinone and Diazetidinone Ring Systems

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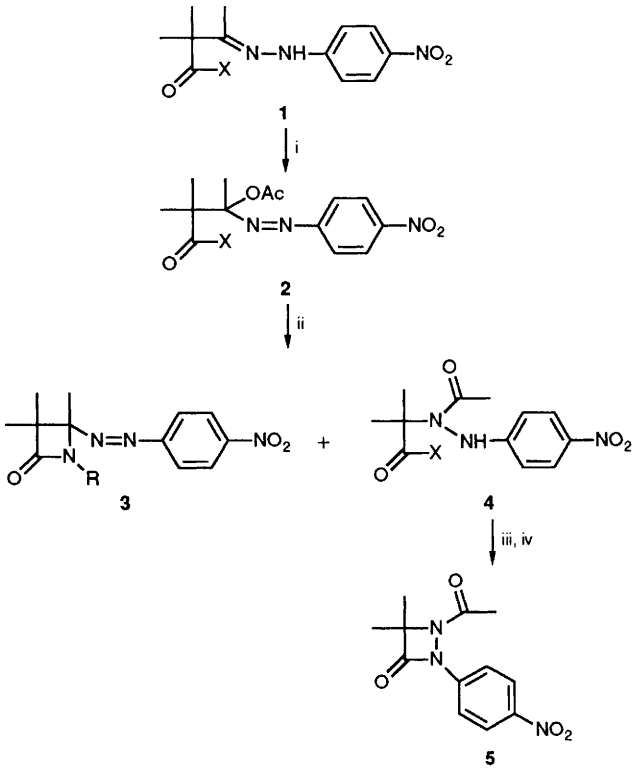
The azoacetates derived from aryl hydrazones of α,α-disubstituted-β-ketoamides are readily transformed into azetidinones or diazetidinones.

Aryl hydrazones ($R^1R^2C{=}N{-}NH{-}Ar$) of ketones are in general readily transformed to azoacetates [$R^1R^2C(OAc){-}N{=}N{-}Ar$] on treatment with lead tetraacetate (LTA), iodobenzene diacetate or thallium triacetate in solvents such as acetic acid and methylene chloride.[1,2] Azoacetates **2** are easily obtained by oxidation of aryl hydrazones **1** derived from β-keto compounds. Acyclic azoacetates have received relatively little attention as substrates for cyclisation to heterocycles with the exception of their transformation to five-membered heterocycles *e.g.* imidazoles and pyrazoles.[3]



a; X = NH-phenyl
b; X = NH-*p*-chlorophenyl
c; X = OEt
d; X = NH_2
e; R = phenyl
f; R = *p*-chlorophenyl
g; R = acetyl
h; X = OH

Scheme 1 *Reagents*: i, lead tetraacetate, methylene chloride; ii, base, acetone or alcohol; iii, NaOH, H_2O; iv, DCC, MeCN

We now report an important contribution to the chemistry of azoacetates **2** which results in their cyclisation to four-membered rings **3** or **5** (see Table 1). Azoacetates **2a–d** are formed in high yield from the corresponding hydrazones **1a–d** and LTA in methylene chloride (>80%). Azoacetates of α,α-dimethylated-β-ketoamides **2a**,**b** cyclise to the azetidin-2-one ring **3e**,**f**, a β-lactam with unusual substitution. Acetylation of the primary amide **2d** allows cyclisation after base treatment to the lactam **3g**. When the reaction of **2a**,**b** with base is carried out in alcohol the β-lactam is accompanied by an unusual rearrangement product **4a**,**b**. The azoacetate **2c** derived from β-ketoester hydrazone **1c** gives an improved yield of the rearrangement product **4c**. The rearrangement is thought to follow deacetylation of the azoacetate. On hydrolysis, **4a–c** give the carboxylic acid **4h** which is readily cyclised to the 1,2-diazetidin-3-one **5**, and represents a new route to this ring system (see Scheme 1).[4] In previous reports on base treatment of azoacetates the products are five-membered rings together with parent ketone and hydrazone.[5]

The generality of the reactions described and their extension to more appropriately substituted structural types is under investigation.

Table 1

	Reagent	Product [yield (%)]
2a	K_2CO_3, acetone	**3e** (28)
2b	K_2CO_3, acetone	**3f** (50)
2a	KCN, propanol	**3e** (44), **4a** (13)
2b	KCN, propanol	**3f** (34), **4b** (44)
2b	KCN, ethanol	**3f** (48), **4b** (25)
2c	KCN, ethanol	**4c** (30)
4a	H^+, H_2O	**4h** (55)
4c	NaOH, H_2O	**4h** (80)
4h	DCC, MeCN[a]	**5** (45)

[a] DCC = 1,3-dicyclohexylcarbodiimide.

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