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The preparation of 1,2,4-triazines from α,β-diketo-ester equivalents and their application in pyridine synthesis

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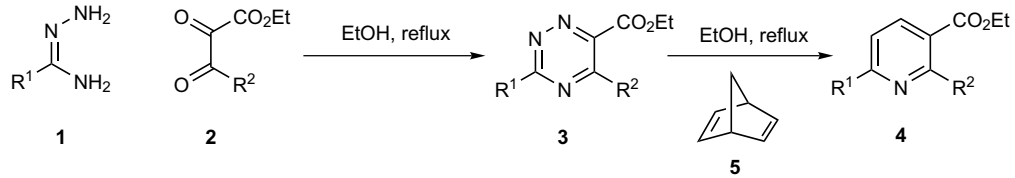
Abstract—The α-Chloro-α-acetoxy-β-keto-esters were prepared from β-keto-esters in good overall yields. These compounds reacted as α,β-diketo-ester equivalents with amidrazones yielding triazines, generally in good yields, or with an amidrazone and 2,5-norbornadiene in a one-pot aza Diels–Alder reaction to give the corresponding pyridines.

Pyridine derivatives occupy a central position in modern heterocyclic chemistry and consequently new and efficient methods for the preparation of this important heterocyclic ring system are of contemporary interest.[1] The aza Diels–Alder reaction has become an important and versatile method for the preparation of pyridine derivatives and several recent reviews have discussed the scope and application of this useful reaction.[2] 1,2,4-Triazines[3] have been used as 2-azadiene equivalents on many occasions and these heterocycles have been reacted with suitable acetylene equivalents, including 2,5-norbornadiene,[4] yielding pyridine derivatives. We have recently described the 'one-pot' reaction of amidrazones **1** ($R^1 = CO_2Et$ or 2-pyridyl) with the α,β-diketo-ester derivatives **2** ($R^2 = Ph$, *n*-Pr or *i*-Pr) in the presence of 2,5-norbornadiene **5** in ethanol at reflux yielding the appropriate pyridine derivatives **4** in good overall yield without isolation of the 1,2,4-triazine intermediates **3** (Scheme 1).[5]

The α,β-diketo-esters **2** were prepared from commercially available β-keto-esters ($R^2COCH_2CO_2Et$) by a diazo-transfer reaction giving the corresponding diazo-compounds [$R^2COC(N_2)CO_2Et$] and subsequent treatment of these with ^tBuOCl.[6] Although these α,β-di-keto-esters **2** are hydrated at the α-carbonyl group, they have been depicted in their keto form for simplicity. From a manufacturing perspective the large scale use of these diazo-compounds would not be attractive and their replacement by other α,β-diketo-ester equivalents would be highly desirable. α,β-Diketo-esters are also commonly prepared by ozonolysis of phosphorane precursors [$R^2COC(=PPh_3)CO_2Et$] and this subject has recently been reviewed by Wassermann and Parr.[7] This



Scheme 1.

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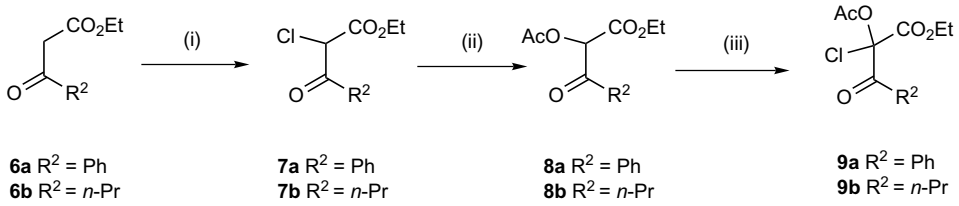

6a R^2 = Ph
6b R^2 = *n*-Pr

7a R^2 = Ph
7b R^2 = *n*-Pr

8a R^2 = Ph
8b R^2 = *n*-Pr

9a R^2 = Ph
9b R^2 = *n*-Pr

Scheme 2. Reagents and conditions: (i) SO_2Cl_2, CH_2Cl_2, rt; (ii) Et_3N, AcOH, DMF, rt; (iii) SO_2Cl_2, CH_2Cl_2, rt.

method of preparing α,β-diketo-esters would generate large quantities of triphenylphosphine oxide as a by-product which would not be desirable on a manufacturing scale.

As a continuation of our previous studies,[5] we have been interested in preparing triazines **3** as substrates for aza Diels–Alder reactions. In view of the limitations described above, we have prepared the α-chloro-α-acetoxy-β-keto-ester derivatives **9a** and **b** as representative examples of α,β-diketo-ester equivalents (Scheme 2). Thus, the α-chloro-β-keto-esters **7a** and **b** were prepared by chlorination of the β-keto-esters **6a** and **b** with sulfuryl chloride[8] and then treatment of products **7a** and **b** with a mixture of acetic acid and triethylamine in dimethylformamide at room temperature yielded the acetates **8a** (95%) and **8b** (90%), reported previously[9,10] by treatment of **6a** and **b**, respectively, with lead tetraacetate. Chlorination of these acetates **8a** and **b** using sulfuryl chloride gave the novel compounds **9a** (77%) and **9b** (98%) as oils that did not require further purification.[11]

Compounds **9a** and **b** were reacted in boiling ethanol solution with a range of amidrazones **1** giving the corresponding 1,2,4-triazine derivatives **3** (Table 1).[12] The best yields were obtained with 2 equiv of the amidrazone. The work-up for this reaction was straightforward; the solvent was evaporated and the residue was taken up into dichloromethane, washed with water and, after drying and evaporating the organic layer, almost pure tri- azines were produced as indicated by ^{1}H NMR spectroscopy.

Additionally, when compounds **9a** and **b** were reacted with 2 equiv of the amidrazone **1** (R^1 = 2-pyridyl) and an excess of 2,5-norbornadiene **5** in ethanol at reflux the corresponding bipyridyls **4** were formed in moderate yield (50% and 63%, respectively), being identical with the compounds described previously.[5c]

Table 1. Preparation of triazines **3**

Triazine **3**		Yield (%)
R^1	R^2	
2-Pyridyl	Ph	98
2-Pyridyl	*n*-Pr	97
Ph	Ph	82
Ph	*n*-Pr	65
SMe	Ph	77
SMe	*n*-Pr	83
Me	Ph	54
Me	*n*-Pr	53

In conclusion, we have prepared the α,β-diketo-ester equivalents **9a** and **b** and shown that these compounds react with amidrazones giving 1,2,4-triazines **3** in good yields.

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11. Compound **9a**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.13 (d, 2H, $J = 7$ Hz, Ph*H*), 7.64 (t, 1H, $J = 7$ Hz, Ph*H*), 7.50 (m, 2H, Ph*H*), 4.31 (q, 2H, $J = 7$ Hz, $-CO_2CH_2CH_3$), 2.23 (s, 3H, $OCOCH_3$) and 1.29 (t, 3H, $J = 7$ Hz, $-CO_2CH_2CH_3$). HRMS (EI^+) for $C_{13}H_{13}ClO_5$: calculated mass of molecular ion: 285.0524 (M+H); measured mass: 285.0526. Compound **9b**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.32 (q, 2H, $J = 7$ Hz, $-COCH_2CH_3$), 2.85 (q, 2H, $J = 7$ Hz, $-COCH_2-$), 2.24 (s, 3H, $-OCOCH_3$), 1.69 (sextet, 2H, $J = 7$ Hz, $-CH_2-$), 1.32 (t, 3H, $J = 7$ Hz, $-CO_2CH_2CH_3$) and 0.96 (t, 3H, $J = 7$ Hz, $-CH_3$). HRMS (EI^+) for $C_{10}H_{15}ClO_5$: calculated mass of molecular ion: 268.0946 ($M+NH_4$); measured mass: 268.0948.
12. All triazine derivatives gave satisfactory ^{1}H NMR spectra and high resolution mass spectra.