Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: W. J. Watkins, G. E. Robinson, P. J. Hogan & D. Smith (1994) A Convenient, One-Stage Transformation of 2,6-Diethyl-4(H)-pyranone to 4-Amino-2,6-diethylpyridine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:12, 1709-1713, DOI: 10.1080/00397919408010173

To link to this article: http://dx.doi.org/10.1080/00397919408010173

SYNTHETIC COMMUNICATIONS, 24(12), 1709-1713 (1994)

A CONVENIENT, ONE-STAGE TRANSFORMATION OF 2,6-DIETHYL-4(H)-PYRANONE TO 4-AMINO-2,6-DIETHYLPYRIDINE

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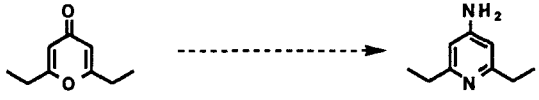
Abstract: The development of the title process and its application on a large scale is described.

During the course of a programme aimed at establishing a convenient way to make 4-amino-2,6-diethylpyridine **2** on a large scale, we were attracted to an approach from the readily available 2,6-diethyl-4(H)-pyranone **1**[1]. Conceptually, the replacement of both oxygen atoms by nitrogen is all that is required (Scheme I).

Scheme I



1 **2**

For the dimethyl analogue, such a transformation has been achieved by treatment of the pyrone or its barium salt with

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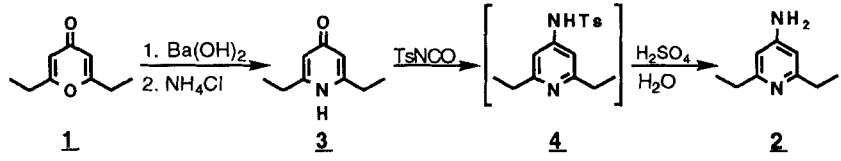
hydroxylamine followed by reduction[2]. In our hands, reaction of the barium salt of 2,6-dimethyl-4(H)-pyranone with hydroxylamine gave 4-(hydroxyamino)-2,6-dimethylpyridine-N-oxide in approximately 60% yield. The same protocol applied to the diethylpyranone, however, gave none of the desired product.

The intermediate barium salt proved to be useful nonetheless. Reaction with ammonium chloride gave the pyridone **3.** Coupled with the facile amination of pyridones or quinolones by treatment with tosyl isocyanate and hydrolysis of the intermediate aminosulphonamide **4**[3], this formed the basis of our first successful approach to the desired aminopyridine **2** (Scheme II):

Scheme II



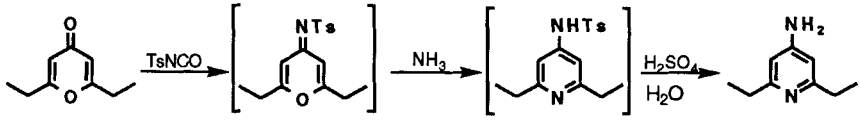
1 **3** **4** **2**

Although this chemistry was used successfully to make 50 Kg of **2**, it suffered from several drawbacks. The most striking of these was the use of barium hydroxide, leading to large amounts of barium chloride-containing effluent. Other alkali metal salts were examined, but with limited success. Another method for amination was clearly required.

Mindful of the ease with which 4(H)-pyranones are protonated at the carbonyl oxygen, we were intrigued by the possibility that reaction with a suitable electrophile might lead to activation of the pyranone/pyrylium ring with respect to nucleophilic attack. This principle has been widely applied in the synthesis of pyridines[4]. An ideal candidate electrophile for our purpose would be tosyl isocyanate (which is cheap and available in bulk), leading to the replacement of the carbonyl oxygen by nitrogen whilst at the same time activating the ring to attack by a nitrogen nucleophile. This chemistry has previously been used in the synthesis of the diphenyl analogue[5].

The sequence as applied in our case is shown in Scheme III.

Scheme III



1 5 4 2

A telescoped process was developed in which **2** was produced in a single stage from **1**. If the starting material had been purified by distillation, toluene proved an ideal solvent and the product was isolated in 61% yield. Crude **1**, however, contained 5-10% 5-ethyl-4-methyl-1,3-resorcinol[6], which also reacted with the isocyanate and led to several impurities. These were minimised when the imine **5** was formed in acetonitrile. The preferred option for large-scale manufacture was therefore to generate **4** in acetonitrile before swapping to toluene for the final hydrolysis.

An unexpected problem was encountered in early experiments when copious amounts of a sublimate were generated during the formation of **4**. This was potentially hazardous for scale up due to the risk of blockages. The sublimate was identified as ammonium carbonate, and was reduced to minimal levels by heating the imine reaction mixture at reflux under reduced pressure to remove dissolved carbon dioxide, prior to the addition of ammonia. Hydrolysis of the sulphonamide group was easily achieved with sulphuric acid containing a small amount of water.

Finally, the high basicity of the product **2** was exploited during the work-up as a means of separation from neutral and acidic impurities. After extraction of the free base into isobutanol/toluene, the hydrochloride salt was extracted into water. The neutral product was then precipitated by the addition of excess sodium hydroxide. In this way 25 Kg of product of >99% strength could be produced per batch, in 68.5% yield from crude **1**.

Although this method was devised solely for the production of 4-amino-2,6-diethylpyridine, it is anticipated that it will prove useful in

the convenient preparation of a variety of symmetrical 4-amino-2,6-disubstituted pyridines.

Experimental:

Preparation of 4-amino-2,6-diethylpyridine

Tosyl isocyanate (134 ml, 1.75 eq) is added dropwise over 1.5-2hrs to a solution of 2,6-diethyl-4(H)-pyranone (76 g, 1.0 eq) in acetonitrile (300 ml) at 60°C with stirring, and the mixture is held at this temperature until reaction is complete (overnight for convenience). A vacuum of ca. 200 Torr is applied and reflux is maintained (50-60°C) for 3 hrs. After cooling to 20°C aqueous ammonia (s.g. 0.88; 70 ml, 2.5 eq) is added. The mixture is warmed slowly to 60°C and the reaction is allowed to proceed to completion (ca. 2.5 hrs). 300 ml solvent is removed by distillation at atmospheric pressure (head temperature 78°C); toluene (300 ml) is added, and distillation is continued until the head temperature is 110°C. A further 300 ml toluene is added and the two-phase mixture is cooled to 60°C before being transferred to a well-stirred solution of water (17 ml) and conc. sulphuric acid (137 ml). The hydrolysis is allowed to proceed to completion at 60°C (overnight for convenience). The mixture is then added over 2 hrs to water (785 ml) with stirring, maintaining the temperature below 70°C (strongly exothermic). Aqueous sodium hydroxide (46% w/w; 35 ml) is added below 70°C, followed by isobutanol (180 ml). After stirring at 60°C for 30 mins, the two phases are allowed to separate, and the lower aqueous phase is extracted with toluene (260 ml). The organic phases are combined and cooled to room temperature. Water (230 ml) is added, followed by conc. hydrochloric acid (100 ml). The mixture is heated at reflux for 15 mins, cooled to room temperature, and filtered (if necessary), washing with water (150 ml). The aqueous phase is separated and diluted with industrial methylated spirit (or ethanol) (110 ml). The pH is adjusted to >11 with aqueous sodium hydroxide (46% w/w; ca. 27 ml). The mixture is heated at reflux for 15 mins, cooled to 0°C and

filtered. The solid product is washed with cold water (2x65 ml) and dried at 60°C overnight, giving a brown solid (51.5g, 68.5% yield).
NMR (270MHz, CDCl3): ∂1.15 (6H, t, J=7Hz), 2.50 (4H, d, J=7Hz), 5.80 (2H, bs), 6.20 (2H, s). MS (EI): 150 (M^+), 149 (100%), 134, 122, 108, 91, 77. Mass measurement: $C_9H_{14}N_2$ requires 150.115699; found 150.114322.

References and Notes:

1. Yates, P.; Hand, E.I.; Singh, P.; Roy, S.K.; Still, I.W.J. *J. Org. Chem.*,**1969**, *34*, 4046. We found that the three-stage method described herein can be reduced to a single stage simply by the gradual addition of water to the hot sulphuric acid/propionic acid reaction mixture containing the initial product. 2,6-Diethyl-4(H)pyranone is formed directly. Separation from the propionic acid can be achieved by adding methanol to the mixture (thereby forming methyl propionate) and distillation. The yield from acetone dicarboxylic acid is 55%.
2. Parisi, F.; Bovina, P.; Quilico, A. *Gazz. Chim. Ital.*, **1962**, *92*, 1138.
3. Bradbury, R.H.; Edwards, M.P.; Ratcliffe, A.H. EP 499415, 19 August 1992.
4. Ellis, G.P., in 'Comprehensive Heterocyclic Chemistry, Vol 3', Boulton, A.J. and McKillop, A., Eds; Pergamon Press, 1984.
5. Van Allen, J.A.; Chie Chang, S.; Reynolds, G.A. *J. Heterocyclic Chem.*, **1974**, *11*, 195.
6. The competitive formation of resorcinol derivatives during the cyclisation of 1,3,5-triketones is well-known. See, for example, Kato, T.; Sato, M.; Kimura, H. *J. Chem. Soc., Perkin Trans. I*, **1979**, 529.

(Received in the UK 17 November 1993)