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# Regiospecific Synthesis of 4-(2-Oxoalkyl)pyridines

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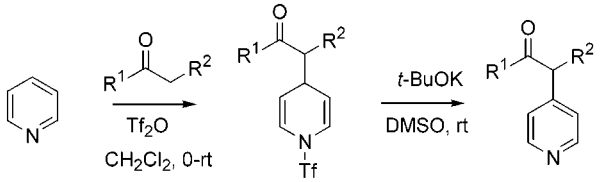
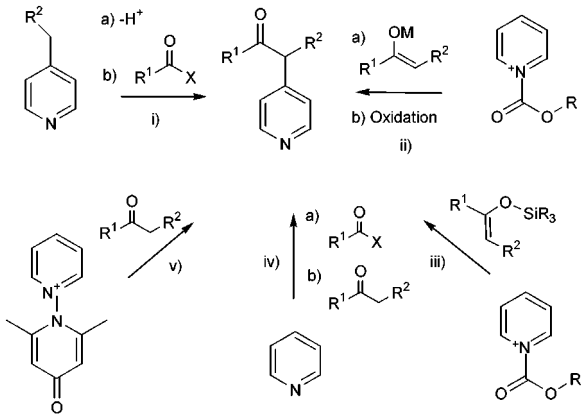
## ABSTRACT




**A new and operationally simple method has been developed for the regiospecific syntheses of 4-(2-oxoalkyl)pyridines from ketones and pyridine in good yields, using triflic anhydride to activate the pyridine ring.**

Functionalization of nitrogen heterocycles constitutes a powerful tool for the synthesis of natural products and bioactive substances. The regioselective introduction of a $\beta$-oxo-alkyl group into the 4-position of a pyridine has attracted considerable attention (Scheme 1): (i) classically, the preparation of 4-(2-oxoalkyl)pyridines involves the treatment of a deprotonated 4-alkylpyridine with an ester or acid chloride.[1] (ii) Comins and Brown have prepared 4- (2-oxoalkyl)pyridines by the treatment of 1-oxycarbonylpyridinium salts with lithium or titanium enolates followed by reaction with sulfur and 5% Pd/C in naphthalene.[2] (iii) Akiba and co-workers reacted trimethylsilyl enol ethers with 1-ethoxycarbonylpyridinium chloride to afford 1-ethoxycarbonyl-4-(2-oxoalkyl)-1,4-dihydropyridines regioselectively.[3] (iv) Doering and McEwen treated ketones with pyridine and benzoyl chloride, or acetic anhydride, to obtain 4-substituted dihydropyridines.[4] (v) Our group developed regiospecific syntheses of 4-substituted (including 4-($\beta$-oxoalkyl)) pyridines via *N*-(2,6-dimethyl-4-oxo-1,4-dihydropyrid-1-yl)pyridinium salt.[5] We now present a practical route for the regiospecific synthesis of 4-(2-oxoalkyl)pyridines using triflic

**Scheme 1**

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(1) (a) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Vol. 2. (b) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, 1996; Vol. 2.

(2) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1984**, *25*, 3297.

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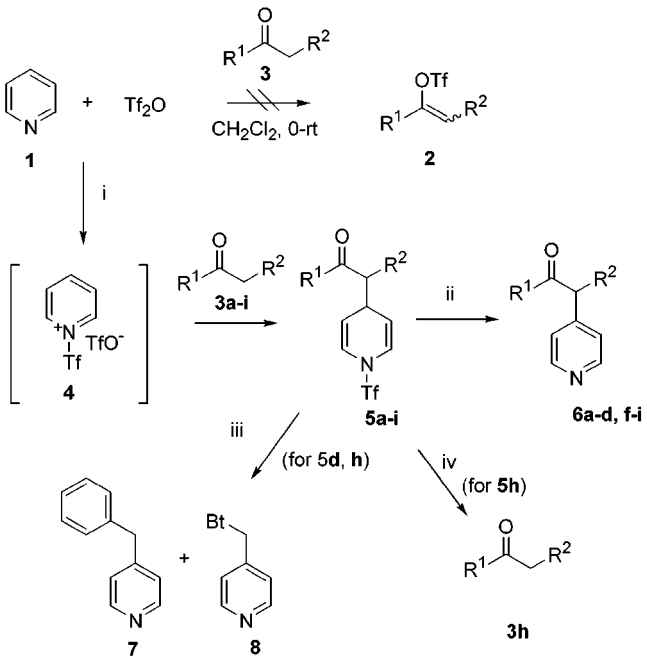
anhydride to activate the pyridine ring, which complements the previous routes and offers an advantage in terms of convenience and yield.

**4-(2-Oxoalkyl)-1,4-dihydropyridines 5a−i.**[6] Treatment of ketones **3a−i** with pyridine **1** (4 equiv) and triflic anhydride (3 equiv) in $CH_2Cl_2$ at 0 °C gave 4-(2-oxoalkyl)-1,4-dihydropyridines **5a−i** (in an average yield of 88%) rather than enol triflates **2** (Scheme 2). No regioisomeric 2-(2-oxoalkyl)-1,2-dihydropyridines were detected from the NMR spectra of the crude products **5a−i**. In the case of **5i**, the starting material **3i** was recovered in 15% yield. The structures of these novel 1,4-dihydropyridines **5a−i** were supported by their NMR spectra, and structure **5f** was confirmed by X-ray crystallography (Figure 1). This crystal structure determination confirmed the regiochemistry of the reaction. The dihydropyridine ring has a conformation similar to those previously reported for three other 1-triflyl-1,4-dihydropyridines.[7]

**Scheme 2**[a]




[a] Conditions and reagents: (i) $CH_2Cl_2$, 0 °C; (ii) *t*-BuOK, DMSO or *t*-BuOH, rt; (iii) TBAF in THF, 70 °C; (iv) KOH in DMSO, 70 °C.

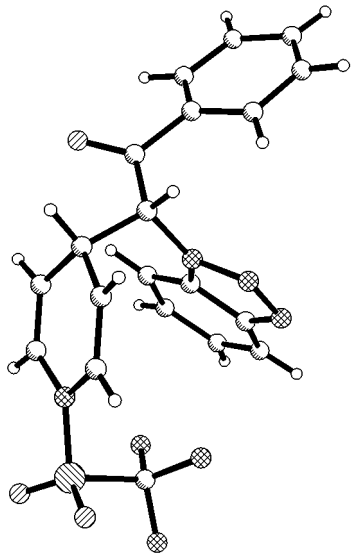


**Figure 1.** Perspective view of the X-ray crystal structure of **5f**.

**Table 1.** 4-Substituted 1,4-Dihydropyridines **5**

| entry | $R^1$ | $R^2$ | mp (°C) | yield (%) |
|---|---|---|---|---|
| **5a** | $(CH_3)_2CH$ | $C_6H_5$ | 44−45 | 96 |
| **5b** | $CH_3$ | $4\text{-}CH_3OC_6H_4$ | 47−48 | 86 |
| **5c** | $4\text{-}BrC_6H_4$ | $C_6H_5$ | 104−105 | 88 |
| **5d** | $C_6H_5$ | $C_6H_5$ | 119−120 | 98 |
| **5e** | $C_6H_4CH_2CH_2$ | | | 81 |
| **5f** | $C_6H_5$ | Bt | 125−126 | 95 |
| **5g** | 2-thienyl | Bt | 138 | 85 |
| **5h** | 2-furyl | Bt | 114−115 | 91 |
| **5i** | $(CH_3)_3C$ | Bt | 125−126 | 72 (15)[a] |

[a] Recovered starting material in parentheses.

**4-(2-Oxoalkyl)pyridines 6a−d,f−i.**[8] 1,4-Dihydropyridines **5a−d,f−i** on treatment with *t*-BuOK in DMSO or *t*-BuOH afforded **6a−d,**[9,10] **f−i** (average 92% yield). Treatment of **5h** with KOH in DMSO at 70 °C gave **3h** in quantitative yield. Pyridine derivative **6e** was not obtained as a result of

(3) (a) Akiba, Y.; Nishihara, Y.; Wada, M. *Tetrahedron Lett*. **1983**, *24*, 5269. (b) Wada, M.; Nishihara, Y.; Akiba, Y. *Tetrahedron Lett*. **1985**, *26*, 3267.

(4) Doering, W. von E.; McEwen, W. E. *J. Am. Chem. Soc.* **1951**, *73*, 2104.

(5) (a) Katritzky, A. R.; Beltrami, H.; Keay, J. G.; Rogers, D. N.; Sammes, M. P.; Leung, C. W. F.; Lee, C. M. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 792. (b) Lee, C. M.; Sammes, M. P.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2458.

(6) **Typical Procedure for the Preparation of 5.** To a cooled (0 °C) solution of a ketone **3** (10 mmol) in $CH_2Cl_2$ (50 mL) was added pyridine (dried over NaOH, 3.2 mL, 40 mmol), and then triflic anhydride (5.0 mL, 30 mmol) was added dropwise over 30 min at 0 °C. The ice bath was removed, and the reaction mixture stirred at room temperature overnight. The reaction mixture was washed with saturated $NH_4Cl$ (2 × 50 mL) and $H_2O$ (2 × 50 mL). The organic layer was dried over $MgSO_4$. The crude products were purified by recrystallization or chromatography to afford the desired 1,4-dihydropyridines **5** in good to excellent yields.

(7) (a) Toscano, R. A.; Hernadez-Galindo, M. del C.; Rosas, R.; Garcia-Mellado, O.; Portilla, F. del R.; Amabile-Cuevas, C.; Alvarez-Toledano, C. *Chem. Pharm. Bull*. **1997**, *45*, 957. (b) Toscano, R. A.; Rosas, R.; Hernadez-Galindo, M. del C.; Alvarez-Toledano, C.; Garcia-Mellado, O. *Transition Met. Chem*. **1998**, *23*, 113.

(8) **Typical Procedure for the Preparation of 6.** To a solution of compound **5** (5 mmol) in DMSO (20 mL) was added *t*-BuOK (1.68 g, 15 mmol) at 10 °C. The reaction mixture was stirred at room temperature for 10−30 min. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with $H_2O$ and dried over $MgSO_4$. Recrystallization from hexanes−ethyl acetate afforded product **6** in 81−97% yields.

(9) Anders, E.; Will, W.; Stankowiak, A. *Chem. Ber*. **1983**, *116*, 3192.

(10) Raynolds, S.; Levine, R. *J. Am. Chem. Soc.* **1960**, *82*, 472.

the instability of compound **5e**. The structures of the pyridine derivatives **6a**−**d**,**f**−**i** were characterized by their NMR and mass spectra. In the $^1$H NMR spectra of **6a**−**d**,**f**−**i** two characteristic doublets ($J$ = ca. 5.5 Hz, 2H) at ca. 8.50 and 7.20 ppm were assigned to the pyridine ring and a characteristic singlet at ca. 6.0 or 7.5 ppm was assigned to the methine group attached to the pyridine moiety.

However, several other attempts to eliminate the triflate group from 4-(2-oxoalkyl)-1,4-dihydropyridines **5** under various reaction conditions, including (i) reflux with isopropylamine, (ii) $NaOCH_3$ in methanol or toluene, and (iii) NaH in THF, failed. Use of TBAF in THF afforded the desired 4-(2-oxoalkyl)pyridine **6f** in 55% yield. In the case of **5d**,**h**, the application of TBAF failed to afford the corresponding products **6d**,**h** and gave instead **7**[11] and **8**, respectively.

In conclusion, we have developed a new and operationally simple method for the regiospecific synthesis of 4-(2-oxoalkyl)pyridines from ketones and pyridine, using triflic anhydride to activate the pyridine ring. This method complements the existing methods as it is highly regioselective and high-yielding.

(11) Chia, W.-L.; Shiao, M.-J. *Tetrahedron Lett.* **1991**, *32*, 2033.

**Table 2.** 4-(2-Oxoalkyl) Pyridines **6**

| entry | $R^1$ | $R^2$ | mp (°C) | yield (%) |
|---|---|---|---|---|
| **6a** | $(CH_3)_2CH$ | $C_6H_5$ | 167−168 | 91 |
| **6b** | $CH_3$ | 4-$CH_3OC_6H_4$ | 114−115 | 81 |
| **6c** | 4-$BrC_6H_4$ | $C_6H_5$ | 235−236 | 97 |
| **6d** | $C_6H_5$ | $C_6H_5$ | 117−118 | 95 |
| **6f** | $C_6H_5$ | Bt | 154−155 | 90 (55)[a] |
| **6g** | 2-thienyl | Bt | foam | 91 |
| **6h** | 2-furyl | Bt | 211−212 | 94 |
| **6i** | $(CH_3)_3C$ | Bt | 153−154 | 95 |

[a] Compound **5f** was treated with TBAF in THF at 70 °C.

**Supporting Information Available:** Characterization data for compounds **5a**−**d**,**f**−**i**, **6a**−**d**,**f**−**i**, **7**, **8**, and X-ray data for **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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