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Facile Regiocontrolled Synthesis of Trialkyl-Substituted Pyrazines

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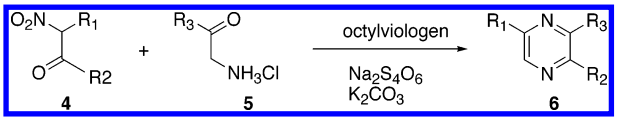
ABSTRACT



α-Nitro ketones can be transformed selectively into trialkyl-substituted pyrazines via reaction with α-amino ketones using octyl viologen as an electron-transfer reagent. The new synthetic method, and the optimal reaction conditions that allow for the regiochemical control, are described.

Alkylpyrazines have been known as flavor components in foods,[1] as versatile synthetic intermediates,[2] and as pheromones in various insect species.[3] From the perspective of chemical ecology, which we are interested in, alkylpyrazines have been recognized as the components of trail laying[4] or alarm pheromones[5,6] in various species of ants.

Alkylpyrazines are produced chiefly by self-condensation of α-amino carbonyl compounds and the combination of α-diketones with vicinal diamines followed by dehydrogenation.[2a] Those methods failed in the preparation of unsymmetrical substituted pyrazines because they afford mixtures of regioisomers.

Substituted alkylpyrazines are challenging targets, and previous methods developed to synthesize this class of compounds regioselectively were unsatisfactory for one reason or the other. To date, the methods used to overcome this problem either use thermal electrocyclization−aromatization, which requires the use of specialist high-temperature short contact pryolysis equipment,[7] or expensive zirconium-mediated complexes.[8] Sato[9] et al. developed a method where 2,5-dimethylpyrazines are alkylated yielding unsymmetrical trialkylpyrizines; however, this method limits the substitution at the 2,5 position to methyl groups.

The synthetic strategy of this method is based on reacting α-nitro ketone with α-amino ketone protected as the hydrochloride salt under reducing conditions, where octylviologen is used as the reducing agent. The use of classic reducing agents to reduce the nitro group of the nitro ketone such as zinc, tin, or iron in the presence of an acid gave a mixture of regioisomers, and in some cases, the reaction stopped at intermediate stage, yielding hydrazines. Octylviologen was chosen on the basis of the work by Hu,[10] where octylviologen was used to reduce a series of substituted nitrobenzenes to substituted anilines.

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(1) (b) Maga, J. A.*Pyrazine in Foods. An Update*; Furia, T. E., Ed.; CRC Critical Reviews In Food Sciences And Nutrition: Boca Raton, FL, 1982; Vol. 16, pp 1−48. (b) Brophy, J. J.; Cavill, G. W. K. *Heterocycles* **1980**, *14*, 477. (c) Seeman, J. I.; Ennis, D. M.; Secor, H. V.; Claweson, L.; Palen, J. *Chem. Senses* **1989**, *14*, 395.

(2) (a) Barlin, G. B. *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1982; Vol. 41. (b) Hasegawa, M.; Katsumata, T.; Ito, Y.; Saigo, K.; Iitaka, Y. *Macromolecules* **1988**, *21*, 3134.

(3) (a) Fales, H. M.; Blum, M. S.; Southwick, E. W.; William, D. L.; Roller, P. P.; Don, A. W.*Tetrahedron* **1988**, *44*, 5045. (b) Tecle, B.; Sun, C. M.; Borphy, J. J.; Toia, R. F. *J. Chem. Ecol* **1987**, *13*, 1811. (c) Wheeler, J. W.; Avery, J.; Olubajo, O.; Shamim, M. T.; Storm, C. B. *Tetrahedron* **1982**, *38*, 1939.

(4) Cross, J. H.; Byler, R. C.; Ravid, U.; Silverstein, R. M.; Robinson, S. W.; Baker, P. M.; DeOliveira, J. S.; Jutsum, A. R.; Cherrett, J. M. *J. Chem. Ecol.* **1979**, *5*, 187.

(5) Brown, W. V.; Moore, B. P. *Insect Biochem.* **1979**, *9*, 451.

(6) Oldham, N. J.; Morgan, E. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2713.

(7) Buchi, G.; Galindo, J. *J. Org. Chem.* **1991**, *56*, 2605.

(8) Guram, A. S.; Jordan, R. F.*J. Org. Chem.* **1992**, *57*, 5994.

(9) Sato, N.; Matsuura, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2345.

(10) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 919.

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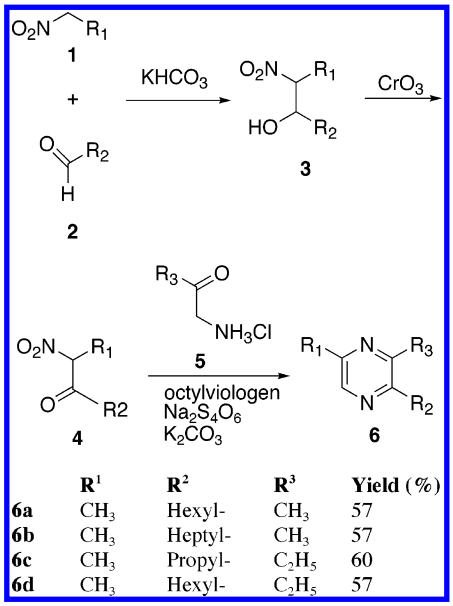
In this method, the α-nitro ketones[11] (**4**) are reacted with suitable α-amino ketones[12] (**5**) in the presence of octylviologen and hydrogen sulfite (see Scheme 1), where

Scheme 1. Synthesis of Trialkylpyrazines **6a**−**d**



	R^1	R^2	R^3	Yield (%)
6a	CH_3	Hexyl-	CH_3	57
6b	CH_3	Heptyl-	CH_3	57
6c	CH_3	Propyl-	C_2H_5	60
6d	CH_3	Hexyl-	C_2H_5	57

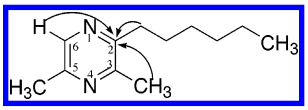
octylviologen serves as the electron-transfer agent. Addition of the α-amino ketone along with the hydrogen sulfite solution to that of the α-nitro ketone and octylviologen solution using a syringe pump ensures that only one regioisomer is formed. Optimization, by systematically changing addition times and rates, revealed that simultaneous addition over 25 min affords a much cleaner product. However, it also revealed that addition of the amino ketone must begin and end 1 min before that of the hydrogen sulfite/potassium carbonate mixture in order to obtain a pure product. Delaying addition of the amino ketone by 1 min ensures that the amino ketone is always in excess, thus preventing reduction and self-condensation of the nitroketone, which would result in a mixture of alkylpyrazines. The use of the syringe pump, which allows for the simultaneous addition of precise quantities of both the α-amino ketone and the hydrogen sulfite solutions over precisely controlled times, is crucial to this method.

(11) The α-amino ketones were prepared by a modified chromate oxidation procedure that minimized reaction time and is scaleable: Elmaaty, T. A.; Castle, L. W. *Molecules* **2005**, in press.

(12) Yinglin, H.; Hongwen, H. *Synthesis* **1990**, 615.

Unequivocal proof of structure for **6a** was accomplished through the concerted interpretation of the ^1H, ^{13}C, gHMQC, and gHMBC NMR spectra. The three key long-range correlations that unequivocally prove the regiochemistry are those of H-6, which resonates at δ 8.19, the 3-methyl protons resonating at δ 2.53, and the 1′ protons of the butyl group resonating at δ 2.77 with the resonance at δ 152.93 corresponding to C-2 (see Table 1).

Table 1. ^1H and ^{13}C NMR Assignments and GHMBC Correlations for **6a**



position	^1H (δ)	gHMBC correlations	^{13}C (δ)
2			152.93
3			150.98
5			149.92
6	8.19	149.92, 152.93	141.12
3-CH_3	2.53	150.98, 152.93	21.83
5-CH_3	2.49	149.92, 141.12	21.24
1′	2.77	152.93, 150.98, 29.92	34.83
2′	1.30 (m)	*a*	29.49[b]
3′	1.30 (m)	*a*	28.65[b]
4′	1.30 (m)	*a*	31.91[b]
5′	1.30 (m)	*a*	22.80
6′	0.88	22.80, 31.91	14.29

[a] Correlations are ambiguous due to chemical shift overlap. [b] These chemical shift assignments are interchangeable; the ^{13}C chemical shift for 4′ was assigned on the basis of correlation with 6′ protons.

In conclusion, a new one-pot synthesis of trialkylpyrazines using readily available starting materials has been developed and proceeds with complete control of regioselectivity. Also, the regiochemistry has been unequivocally established using 2D-NMR methods.

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Supporting Information Available: Selected spectral data including ^1H NMR, ^{13}C NMR, gCOSY, gHMBC, and gHMQC for the synthesized compounds. Detailed experimental procedures and spectral/physical data are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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