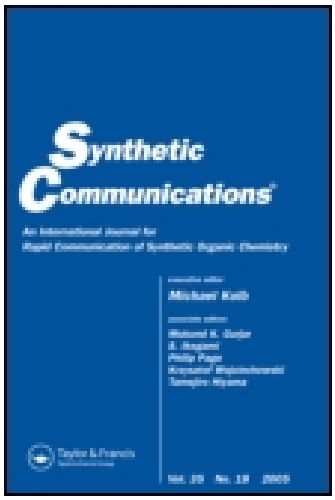

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Microwave Assisted Improved Synthesis of 6-Formylpterin and Other Heterocyclic Mono- and Di-aldehydes

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Published online: 17 Aug 2006.

To cite this article: Shyamaprosad Goswami & Avijit Kumar Adak (2003) Microwave Assisted Improved Synthesis of 6-Formylpterin and Other Heterocyclic Mono- and Di-aldehydes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:3, 475-480, DOI: 10.1081/SCC-120015779

To link to this article: http://dx.doi.org/10.1081/SCC-120015779

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 3, pp. 475–480, 2003

Microwave Assisted Improved Synthesis of 6-Formylpterin and Other Heterocyclic Mono- and Di-aldehydes

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ABSTRACT

2-Pivaloylamino-6-formylpterin (**1a**) and a series of other important heterocyclic aldehydes (**2a**, **3a**, **4a**, **6a**, and **7a**) have been synthesized in good yield by microwave assisted selenium dioxide oxidation. Interestingly, 2-methylpyrazine gives 2-pyrazinecarboxylic acid (**5a**) under the similar condition.

Key Words: Selenium dioxide; 6-formylpterin; Heterocyclic aldehyde; Microwave.

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DOI: 10.1081/SCC-120015779 0039-7911 (Print); 1532-2432 (Online)

Microwave assisted organic reactions[1] have been widely studied in various chemical reactions e.g., condensation, addition, cross-coupling reaction, cyclo-addition, aromatic substitution, esterification, oxidation and reduction etc. However, selenium dioxide oxidation of allylic methyl to aldehyde group in heterocyclic compounds in solvent free condition remains unexplored. Heterocyclic aldehydes are important intermediates for the synthesis of biologically active molecules. 6-Formylpterin is a precursor of the pteridine substrate of dihydropteroate biosynthesis.[2] In our synthetic studies[3] on molybdenum cofactor[4] which has a C6-substituted pterin ring system, we found this procedure is efficient and economic for the synthesis of 6-formylpterin.

RESULTS AND DISCUSSION

For the first time, we report here a useful, straightforward and economic procedure for the synthesis of 2-pivaloylamino-6-formylpterin (**1a**), a new functionalized pyridine aldehyde (2-pivaloylamino-pyridine-6-carboxaldehyde, **3a**) and a series of other important heterocyclic mono- and di-aldehydes (**2a**, **4a**, **6a** and **7a**) in microwave condition.

The yields are better than conventional heating of the compounds with selenium dioxide in suitable solvents like dioxan, pyridine or acetic acid. Microwave assisted selenium dioxide oxidation is found to be much better in terms of improved reaction rates, less hazardous work-up and formation of cleaner products. However, in case of 2-methylpyrazine the only isolated product is 2-pyrazinecarboxylic acid (**5a**). Alkaline hydrolysis of **1a** and **3a** afforded the corresponding amino aldehydes. The reaction conditions and yields are summarized in Table 1. All the compounds are well characterized by ^{1}H NMR and other spectroscopic studies. Their melting points and NMR-spectra (for known compounds) were compared with those reported[5–7] (see experimental).

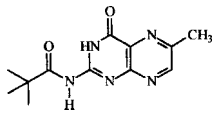
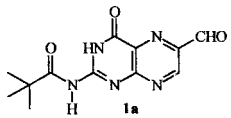
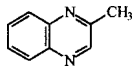
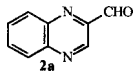
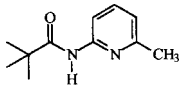
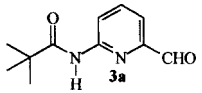
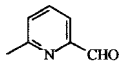
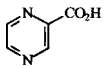
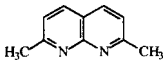
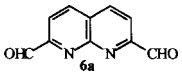
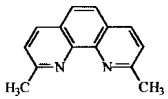
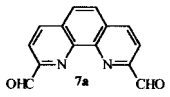
In conclusion, we have developed an efficient new route for the synthesis of a series of heterocyclic mono- and di-aldehydes which takes very short time for completion compared to conventional procedures.

EXPERIMENTAL

General Procedure for Conversion of Aromatic Methyl to Aldehyde

The compound with stoichiometric amounts of selenium dioxide was mixed thoroughly in a conical flask (for Entry 1 the mixture was moistened

Table 1. Products of microwave[a] assisted SeO_2 oxidation.

Entry	Starting material	Product	Reaction condition	Yield[b]	reference
1		 **1a**	750 W, 15 min	60%	5
2		 **2a**	450 W, 12 min	90%	6
3		 **3a**	450 W, 25 min	40%	—
4		 **4a**	450 W, 15 min	60%	—
5		 **5a**	450 W, 5 min	50%	7a
6		 **6a**	450 W, 12 min	90%	7b
7		 **7a**	450 W, 10 min	85%	7c

[a]A domestic BPL Microwave Oven (800 G) was used.
[b]Isolated yields of chromatographically pure material.

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with glacial acetic acid and for Entries 4, 6 and 7 the mixture was moistened with dioxan) and was irradiated in the microwave oven which resulted a solid mass. The solid was dissolved in chloroform, filtered through a pad (3–4 cm) of celite and washed well with chloroform. The combined filtrate and washings were evaporated to dryness by the rotary evaporator and purified by column chromatography using silica gel (60–120 or 100–200 mesh), afforded the corresponding mono- and di-aldehydes.

Representative Procedure for Conversion of 2-Methylquinoxaline to Quinoxaline-2-carboxaldehyde

A mixture of 2-methylquinoxaline **2** (1.01 g, 7.01 mmol) and selenium dioxide (0.84 g, 7.71 mmol) was irradiated at 450W for 12 min which produced a solid mass. The residue left was dissolved in chloroform and filtered through a pad (3–4 cm) of celite. The filtrate was evaporated to dryness by the rotary evaporator and purified by column chromatography (silica gel, 100–200 mesh) using chloroform–petroleum ether (3:1) as an eluent ($R_f = 0.3$) which afforded white crystalline solid **2a** (0.98 g, 90%). M.p. 68–69°C (lit.[6] 109°C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.22 (s, 1H), 9.36 (s, 1H), 8.19 (d, 1H, $J = 8.3$ Hz), 8.15 (d, 1H, $J = 8.3$ Hz), 7.89–7.82 (m, 2H). Mass (FD): 158 (M^+).

^{1}H NMR for Selected Compounds

Compound 1a: M.p. 246–247°C (lit.[5] 247–248°C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.52 (br s, 1H), 10.26 (s, 1H), 9.40 (s, 1H), 8.55 (br s, 1H), 1.36 (s, 9H). ^{1}H NMR reported in literature:[5] δ 12.51 (br, 1H), 10.28 (s, 1H), 9.42 (s, 1H), 8.59 (br, 1H), 1.38 (s, 9H).

Compound 3a: M.p. 88–90°C (uncorrected). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.8 (s, 1H), 8.45 (d, 1H, $J = 8.3$ Hz), 8.17 (bs, 1H), 7.95 (d, 1H, $J = 7.4$ Hz), 7.84 (t, 1H, $J = 7.9$ Hz), 1.35 (s, 9H). Anal. Calcd for $C_{11}H_{14}N_2O_2$: required C, 64.04; H, 6.84; N, 13.58. Found: C, 64.00; H, 6.88; N, 13.32.

Compound 4a: M.p. 38–39°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.16 (s, 1H), 8.17 (d, 1H, $J = 7.6$ Hz), 8.08 (t, 1H, $J = 7.6$ Hz), 7.76 (d, 1H, $J = 8.0$ Hz), 2.66 (s, 3H).

Compound 5a: M.p. 218–219°C dec. (lit.[7a] 219°C dec.). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.35 (d, 1H, $J = 1.0$ Hz), 8.71 (d, 1H, $J = 2.3$ Hz), 8.49 (s, 1H).

Compound 6a: M.p. 221–223°C (lit.[7b] 224–225°C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.36 (s, 2H), 8.50 (d, 2H, $J = 8.2$ Hz), 8.26 (d, 2H, $J = 8.3$ Hz). ^{1}H NMR (DMSO-d_6) reported in literature[7b]: δ 8.30 (H-3, 8), 8.75 (H-4, 7), 8.25 (H-5,6), 10.45 (CHO).

Compound 7a: M.p. 228–230°C (lit.[7c] 231–232°C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.55 (s, 2H), 8.53 (d, 2H, $J = 6.0$ Hz), 8.38 (d, 2H, $J = 9.0$ Hz), 7.95 (s, 2H). ^{1}H NMR (DMSO-d_6) reported in literature[7c]: δ 8.21 (d, H-3,6; 2H, $J_{3,4} = 8.0$ Hz), 8.85 (d, H-4,5; 2H), 10.21 (s, CHO, 2H).

ACKNOWLEDGMENTS

We thank CSIR, Government of India for financial support and Bose Institute, Kolkata for NMR facility. We also acknowledge the help of Reshmi Mukherjee in our laboratory. We wish to thank Professor Thomas Schrader of Philipps-Universitat, Marburg, Germany for the mass spectrum. A. K. A. thanks CSIR, Government of India for providing him a Senior Research fellowship.

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Received in the USA February 19, 2002