A FACILE AND HIGHLY STEREOSELECTIVE SYNTHESIS OF (2E)-, (2E,4E)-UNSATURATED AMIDES AND RELATED NATURAL PRODUCTS¹

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Abstract: A facile synthesis of (2E)-, (2E, 4E)-unsaturated amides was achieved via arsonium bromides with high stereoselectivity. Its application to the synthesis of related natural products **4** and **5** is also reported.

(2E)-, (2E,4E)-Unsaturated amides belong to an important class of natural products which show both physiological and insecticidal activities.² There have appeared several methods for their synthesis involving Wittig reaction, Knoevenagel condensation or the double elimination reaction.³ Nevertheless, all of them involve multiple steps to approach the target molecules.

Recently, we have reported a facile synthetic method for α,β -unsaturated aldehydes via arsonium bromide employing potassium carbonate as a base.⁴ In our continuing study on arsonium reagents, we have found that (2E)-, (2E,4E)unsaturated amides are easily accessible from various aldehydes with high stereoselectivity by means of organoarsonium bromides. The outline of our method is illustrated in **Scheme 1**, and the results are summarized in **Table 1**.

Scheme 1

 $R(CH=CH)_{n}CHO + Ph_{3}ASCH_{2}CNR^{1}R^{2}Br \xrightarrow{\text{THF or }CH_{3}CN/\text{trace }H_{2}O} R(CH=CH)_{n+1}CNR^{1}R^{2} R^{2}$ $Ia n=0; \qquad 2a R^{1}R^{2}=-(CH_{2})_{4}- 3a R^{1}R^{2}=-(CH_{2})_{5}- 3b R^{1}R^{2}=-(CH_{2})_{5}-$

The reagents 2a and 2b were easily prepared. Thus triphenylarsine reacted with readily available 2-bromoacetyl pyrrolidine and 2-bromoacetyl piperidine in benzene under reflux for 5-6 hrs in 85% and 96% yields, respectively.⁵ These two reagents 2a and 2b reacted with saturated aldehydes 1a to afford (2E)-unsaturated amides, or reacted with (E)- σ , β -unsaturated aldehydes 1b to afford (2E, 4E)-dienamides smoothly in excellent yields. The simplicity of the reaction procedure, the mildness of reaction conditions (room temperature, weak basicity), high stereoselectivity and excellent yields enable the reaction to be a practical appraoch to synthesis of naturally occurring unsaturated amides.

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The following procedure is representative. Reagent 2b (l.2mmol), benzaldehyde(l.0 mmol), and potassium carbonate(l.2 mmol) were mixed in 10 ml anhydrous THF ($30,Al H_20$), and stirred at 25°C for 6 hr. The reaction mixture was passed through a short column of silica gel to remove most of triphenylarsine oxide and inorganic salts. The desired product (PhCH=CHCON) was obtained after chromatography in 98% yield and no Z isomer was detected in ¹H NMR spectrum. The results are shown in **Table 1**.

Entry	Reactant 1	Product 3 ⁱⁱ	Reaction Time(hr)	Yield (%) iii
1	р-02N-С6Н4СНО	p-02N-C6H4CH=CHCON	9	81
		p-02N-C6H5CH=CHCON	8	98
2	с ₆ н ₅ сно	C6H5CH=CHCON	10	95
		C6H5CH=CHCON	6	98
		\square		
3	СНО	CH=CHCON	4	98
	\wedge	CH=CHCON	4	97
4	Сно	CH=CHCON	9	95
		CH=CHCON	9	96
5	n-C ₆ H ₁₃ CHO	n-C ₆ H ₁₃ CH=CHCON	10	96
		n-C ₆ H ₁₃ CH=CHCON	8	99
6	с6н5сн=снсно	C ₆ H ₅ (CH=CH) ₂ CON	8	90
		C_6H_5 (CH=CH) 2CON	13	83
7	сн ₃ сн=снсно	CH ₃ (CH=CH) ₂ CON	12	88
8	n-С ₅ Н ₁₁ СН=СНСНО	n-C ₅ H ₁₁ (CH=CH) ₂ CON	7	82

Table 1 The Reaction of 1 with 2a and 2b¹

- Reaction of 1 with 2a was carried out in CH₃CN and with 2b was carried out in THF. All the reactions were run at 25°C.
- ii. All compounds were confirmed by ${}^{1}\text{H}$ NMR, IR, MS and no Z stereoisomer was found by ${}^{1}\text{H}$ NMR.
- iii. Isolated yields after column chromatography.

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We have applied this method to the synthesis of tetradeca-2E,4E-dienoic acid pyrrolidide 4 naturally occurred in Achillea Arten⁶ and 7-(thiophene)-2E, 4E,6E-heptatrienoic acid piperidide 5 isolated from Otanthus maritima.⁷ Scheme 2 illustrates our approach.

Formylolefination of **6** was achieved according to our procedure, ⁴ and afforded the intermediate **8** in 90% yield (E isomer > 98%, determined by GC). Compound **8** was subjected to the present reaction to give **Achillea amide 4** with high stereoselectivity (no other stereoisomers were detected in ¹H NMR spectrum) in 82% yield.⁸

2-Thiophenecarbaldehyde **9** was treated with formylallyltriphenylarsonium bromide 10^9 in the presence of potassium carbonate to give compound 11 in 79% yield (2E,4E isomer > 95%). 11 was reacted with 2b under the present conditions to afford **Otanthus maritima** amide **5** with high stereoselectivity (no other stereoisomers in ¹H NMR spectrum) in 98% yield.¹⁰ mp. 93-94°C [lit.⁷ 96.5°C]. It is noteworthy that the analog of **4**, trichonine 12, has been synthesized through a four step consecutive reaction in 27.5% overall yield.¹¹ Compound **5** has been synthesized by a six step reaction in 3% overall yield.⁷

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References and Notes

- 1. This paper is the 56th report on the studies of the application of elementoorganic compounds of the fifth and sixth groups in organic syntheses.
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- 5. The reagents 2a and 2b gave satisfactory elemental analysis(C,H: ±0.3%; N, Br:±0.5%).2a: m.p. 191-2°C(from CH₂Cl₂-CH₃CO₂Et); ¹H NMR(60M Hz,CDCl₃/TMS, δ) 7.64(m, 15H), 5.58(s, 2H), 3.95(t, CONCH₂, 2H) and 3.30(t, CONCH₂, 2H), 1.90(m, 4H); IR(KC1) 1440, 1620 cm⁻¹. 2b: m.p. 167-8°C (from CH₂Cl₂-CH₃CO₂Et); ¹H NMR (60M Hz, CDCl₃/TMS, δ) 7.70(m, Ar-H, 15H), 5.70(s, 2H), 3.81(m, CONCH₂, 2H) and 3.35(m, CONCH₂, 2H), 1.55(m, 6H); IR(KC1) 1620, 1460, 1380 cm⁻¹.
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- 8. Achillea amide 4 $CH_3(CH_2)_8CH=CH-CH=CHCON$: colourless oil. ¹H NMR (200M Hz, $CDCl_3/TMS, \delta$) 0.88(t, 3H), 1.26(m, 14H), 1.91(br., s, 4H), 2.17(m, 2H), 3.53(m, 4H), 6.08(d, $J_{2,3}=15$ Hz, 1H, H-2), 6.0-6.25(m, H-4, 5, 2H), 7.28(dd, $J_{2,3}=15$ Hz, $J_{3,4}=11$ Hz, 1H, H-3). IR(neat) 2900, 1650, 1620, 990 cm⁻¹. MS m/z (rel. int.) 277(34) [M]⁺, 207(10) [M-NC_4H_8]⁺, 178(16) , 164(16) [M-C_8H_{17}]⁺, 150(100) [M-C_9H_{19}]⁺, 98(21) [C_4H_8NCO]⁺
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- 10. Otanthus maritima amide 5: yellow solid, ¹H NMR(200M Hz, CDCl₃/TMS, \$) 1.63
 (m, 6H), 3.58(m, 4H), 6.38(d, J_{2,3}=14.7 Hz, 1H, H-2), 7.35(dd, J_{2,3}=14.7Hz,
 J_{3,4}=10.8 Hz, 1H, H-3), 6.48-7.20(m, 7H, H-4, -5, -6, -7 and H-thiophene 7H);
 IR(KCl) 1640, 1605, 1575, 1440, 1005 cm⁻¹; MS m/z (rel. int.) 274(100)
 [M+1]⁺, 273(95) [M]⁺, 189(28)[M- NC₅H₁₀]⁺, 161(36)[M-CONC₅H₁₀]⁺, 128(39),
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