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HECK REACTION: STEREO SELECTIVE SYNTHESIS OF TRISUBSTITUTED OLEFINS: USEFUL INTERMEDIATES FOR ANTHRAQUINONE CARBOXYLIC ACID DERIVATIVES

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Abstract: Palladium catalyzed arylation of dialkyl itaconate in presence of $Pd(OAc)_2/PPh_3$ as a catalyst, afforded trisubstituted olefins stereo selectively. These alkenes are useful intermediates for the synthesis of anthraquinone carboxylic acid derivatives. A new coumarin is also synthesized using this protocol.

Palladium catalyzed coupling reaction of Heck type is the most versatile method for C-C bond formation.¹ Application of Heck reaction in the synthesis of natural and non-natural products is well reviewed by Meijere and Meyer.² A very few reports are available in literature about the steroselective synthesis of trisubstituted olefins.^{3,4}

We report herein a simple, direct and steroselective method for the synthesis of trisubstitute olefins using Heck reaction of dialkyl itaconate with bromo aromatics (Scheme-1).

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Scheme -1



The arylated olefins (7-12) are the intermediates for the synthesis of anthraquinone carboxylic acid derivatives (1a-d), agents for the treatment of connective tissue disorders such as rheumatoid arthritis, osteoporosis and cancer.⁵



The synthesis of butenoic acid derivative (3) was attempted by Gallagher et al.^{5a} Starting from naphthyl tin (2) and methyl 2-bromomethyl fumarate using palladium catalyst under a variety of conditions (Scheme-2), but failed to produce any coupled product. This could be explained by the allylic rearrangement of bromomethyl fumarate.⁶ Hence, we were prompted to choose dialkyl itaconate as an olefin in Heck reaction.

2-Bromo-1,4-dimethoxybenzene (4) was prepared from 1,4-dimethoxybenzene with bromine in CCl₄ at 80° C for 5hrs. The bromo compounds (5 and 6) were prepared starting from readily available 1,5-dihydroxynaphthalene,

Scheme-2



bis methylation followed by monodeprotection⁷ and selective bromination at C_2 gave bromophenol,⁸ which was further converted to methyl ether (5) and benzyl ether (6) by reaction with methyl iodide and benzyl bromide respectively.⁹

The reaction of aryl bromides with dialkyl itaconate in presence of $Pd(OAc)_2/PPh_3$ (15 mol%) in DMF and Et_3N resulted arylsubstituted olefins in good yield and the results are presented in table-1.

All the reactions showed 'E' stereoselectivity and Gas Chromatography -Mass Spectrometry (GC/MS) analysis of the products confirmed >95% of 'E' isomer. The stereochemistry of the products was proved by NOE studies.¹⁰

The product selectivity could be explained by the syn addition of arylpalladium halide complex across the olefin followed by syn elimination of **HPdX** through the following conformation.



Standardization of Heck reaction led to the formation of an interesting coumarin acetic acid derivative 13. The reaction of aryl bromide with diethyl itaconate in presence of $Pd(OAC)_2/PPh_3$ (30mol%) in DMF & Et₃N resulted coumarin 13, in 50% yield in addition to the coupled product 11 (20%).

Entry	Ar - Br	Itaconate	Arylated olefins ^C	Yield (%) ^b
1	O CH3 Br	Et00C	OCH3 COOEt	71
2	OCH3 I Br OCH3 4		0CH3 COOEt 0CH3 8	70
Э	OCH3 OCH3 OCH3	м	0CH3 COOEt 0CH3 9	68
4	*	Me0 OC	0CH3 C00Me C00Me C00Me	67
5	OCH ₂ Ph Br OCH ₃ 6	Et 00'C	OCH2Ph COOEt OCH3 11	66.S
6	OCH2Ph Br OCH3	Me00C	00H2Ph COOMe 0CH3 12	65

Table 1 Palladium catalyzed conversion of aryl bromide to arylated olefins.⁰

a With 15 mol% Pd (OAc)2 and PPhs (30 mol%) at 100°C for 16 to 18 hrs.

^b Yields are based on analytically pure isolated compounds after column, chr

^{c°} The structure of olefins were confirmed by ¹H-NMR and MS¹¹

Various synthetic routes to coumarins are known¹² but employ harsh conditions. Low yields were observed. We report here in a new novel & direct method for coumarin synthesis, which utilizes readily available reagents & mild conditions affording good yields.



Typical reaction procedures:

A mixture of bromo compound, 5 (2.5 g, 0.0093 M), diethyl itaconate (1.64 g, 0.0093 M), Pd (OAc)₂ (15 mol% 0.312 g) and triphenylphosphine (30 mol%, 0.729 g) were taken in DMF (20 ml) and flushed thoroughly with argon gas. 10 ml of triethylamine was introduced into the mixture and the reaction mixture was heated to 100° C, and stirred for 18 hrs under argon atmosphere. The dark reaction mixture was cooled to RT and filtered through whatman filter paper and washed with 50 ml of CH₂Cl₂. The filtrate was concentrated at 50°C under reduced pressure. The residue was purified by column chromatography over silica gel using hexane and ethylacetate (10:0.5 v/v) as eluent. Yield 1.75 g, 70%. The structure of the product, **9** was confirmed by spectral data.¹³

The olefin esters, 7-12 were hydrolyzed to the corresponding acids by refluxing for 1 hr in 10% methanolic KOH solution and the melting points of the acids were measured.¹⁴

We therefore present this novel application of Heck reaction for the synthesis of trisubstituted olefins for the first time, which is not only direct and efficient method but also gives, highly stereoselective products in good yields.

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References and Notes:

- 1. Heck, R.F. J. Am. Chem. Soc. 1968, 90, 5518.
- Meijere, Armin De; Meyer, Frank E. Angew. Chem. Int. Ed.Eng. 1994,33, 2379.
- 3. Miyayura, Norio; Suzuki, A. J.C.S. Chem. Commun. 1979, 866.
- 4. Agrios, Konstantinos, A.; Srebnik Morris, J. Org. Chem., 1993, 15, 444.
- a) Gallagher, Peter T.; Hicks Terry A.; Light Foot, Andrew P.; Owton W.M. Tet. Lett., 1994, 35 (2), 289.
 - b) Owton, W.M. J.C.S. Perkin Trans., 1994, 1.
 - c) CA 122: 213773 d; Gallagher, P.T.; Hick T.A.; Owton W.M. Eur. Pat. Appl. EP 638, 540 (Cl. O2), C07C66/15 Feb. 1995.
 - d) CA 122;214082q; Gallagher, P.T., Hick T.A.; Owton, W.H. Eur. Pat. Appl. EP 638, 562 (Cl C07D257/04) 15 Feb. 1995.
- Yashida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.: Uchida, T.; Kumada, M. Organometallics, 1982, 1, 542.
- a) Hannan, R.L.; Barben, R.B.; Rappaport, H. J. Org. Chem., 1979, 44, 2153.
 - b) Alternatively 1-methoxy 5-naphthol was also prepared in 40 % yield starting from 1,5-dihroxynaphthalene and 0.5 eq. of Mel/acetone, K₂CO₃ at RT for 10 hrs.
- 8. Carter A.H.; Race, E.; Rawe, F.M. J. Chem. Soc., 1942, 236.
- 9. Jung, M.E.; Hagenah, J.A. J. Org. Chem., 1987, 52, 1889.
- C₃-methylene hydrogens and 3'H of aryl moiety in all the products showed NOE relationship.
- Compound 13: m.p 212°C ¹H NMR (200 MHz, CDCl₃ δ 1.3 (3H, t) 3.68 (2H, s), 4.05 (3H, s), 4.25 (2H, q), 7.0 (1H, d), 7.45 (1H, d), 7.58 (1H, t), 7.85 (1H, s), 8.15 (2H, d). EIMS m/z 312 (100%).
- Ronald G. Harvey, Cecilia Cortez, Ananthanarayan & Sanford Schmolka; J. Org. Chem., 1988, 53, 3936.

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- 13. Compd. 7: ¹H NMR (200 MHz, CDCl₃) δ 1.3 (6H, m), 3.4 (2H, s), 3.75 (3H, s), 4.25 (4H, m), 6.91-7.3 (4H, m). EIMS: m/z 292 (M⁺, 100%). Compd. 8: ¹H NMR (400 MHz, CDCl₃) δ 1.22 (3H, q), 1.26 (3H, q), 3.42 (2H, s), 3.74 (3H, s), 3.79 (3H, s), 4.19 (2H, q), 4.28 (2H, q), 6.84 (3H, m), 7.9 (1H, s). EIMS: m/z 322 (M⁺, 100%). Compd. 9: ¹H NMR (400 MHz, CDCl₃) δ 1.2 (3H, t), 1.3 (3H, t), 3.26 (2H, s), 3.81 (3H, s), 3.9 (3H, s), 4.1 (2H, q), 4.22 (2H, q), 6.66 (1H, d), 6.81 (1H, d), 7.18 (1H, d), 7.26 (1H, t), 7.82 (1H, d), 8.58(1H, s). EIMS: m/z 372 (M⁺, 100 %). Compd.11: ¹H NMR (200 MHz, CDCl₃) δ 1.27 (6H, m), 3.55 (2H, s), 4.05 (3H, s), 4.2 (4H, m), 5.04 (2H, s), 6.96-8.1 (10H, m), 8.2 (1H, s). EIMS: m/z 448 (M⁺, 5%).
- 14. The Melting Point of the acids from the esters 7, 8, 9 and 11 are 95°C, 98°C, 208°C and 145°C respectively.

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