

Dimethyl Sulfide Induced [3 + 2] Annulation Strategy: An Efficient Synthesis of Functionalized Dihydropyrazole Derivatives Using the Baylis–Hillman Bromides

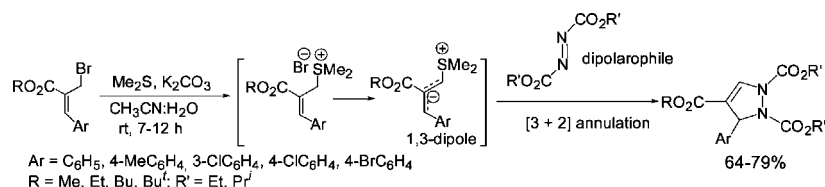
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ABSTRACT



Baylis–Hillman bromides have been successfully employed as a valuable source of 1,3-dipoles for cycloaddition onto dialkyl azodicarboxylates (dipolarophiles) under the influence of dimethyl sulfide and potassium carbonate to provide functionalized dihydropyrazole derivatives in a simple one-pot [3 + 2] annulation strategy.

The pyrazole framework belongs to an important class of heterocyclic compounds possessing pharmacological properties such as antiviral, antitumor, anti-inflammatory, and antimicrobial activities.¹ Certain 1*H*-pyrazole-4-carboxylic esters are known to exhibit antimicrobial activity and are also found to act as intermediates for agrochemical micro-

bicides and herbicides.² Because of the remarkable medicinal and pharmacological potential of pyrazole derivatives, development of simple and efficient methodologies for synthesis of these compounds with different substitution profiles has been and continues to be a challenging and attractive endeavor in organic and medicinal chemistry.^{1b–d,3} Recently, some interesting publications appeared from the research groups of Wang^{3a} and Nair^{3b,c} on the application of Huisgen zwitterions for the synthesis of pyrazole derivatives. Fascinated by these reports and also in continuation of our interest in the heterocyclic compounds⁴ we report herein a simple, facile, and one-pot synthesis of functionalized dihydropyrazole derivatives via [3 + 2] annulation strategy using the Baylis–Hillman bromides as a source of

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Table 1. Standardization: Reaction of Methyl (2Z)-2-Bromomethyl-3-phenylprop-2-enoate (**1a**) (1 mmol) with Diethyl Azodicarboxylate (**3a**) (1 mmol) under the Influence of Me₂S and a Base at Room Temperature To Provide the Dihydropyrazole Derivative (**4a**)

entry	Me ₂ S (mmol)	base (1 mmol)	solvent system	time (h)	yield ^a (%)
1	1.5	K ₂ CO ₃	THF (1 mL)	72	30
2	1.5	K ₂ CO ₃	THF (1 mL)/H ₂ O (0.01 mL)	72	29
3	1.2	K ₂ CO ₃	CH ₃ CN (1 mL)/H ₂ O (0.01 mL)	36	57
4	1.2	K ₂ CO ₃	CH ₃ CN (1 mL)/H ₂ O (0.1 mL)	7	74
5	1.5	K ₂ CO ₃	CH ₃ CN (1 mL)/H ₂ O (0.2 mL)	7	72
6	1.5	NaOH	CH ₃ CN (1 mL)/H ₂ O (0.1 mL)	12	36

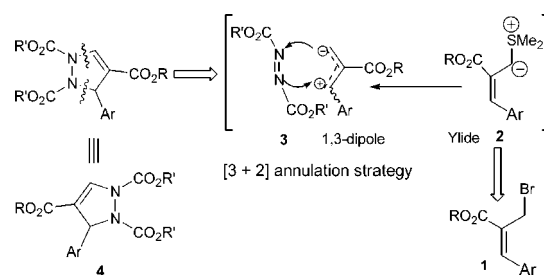
^a Isolated yields of product **4a**.

1,3-dipoles under the influence of dimethyl sulfide and potassium carbonate, in reaction with dialkyl azodicarboxylates as dipolarophiles.

In recent years the Baylis–Hillman reaction has become a popular atom-economy carbon–carbon bond forming reaction in organic chemistry because it provides useful classes of densely functionalized molecules in an operationally simple procedure.^{5,6} Recently, the Baylis–Hillman bromides/acetates have been conveniently transformed into carbocyclic derivatives via the phosphine catalyzed (phosphorus ylides based) [3 + 6] and [3 + 2] annulation strategy.⁷ Also sulfur ylides⁸ derived from the Baylis–Hillman bromides have been employed for the synthesis of cyclopropane and aziridine derivatives.⁹ The Baylis–Hillman adducts have been successfully used for synthesis of pyrazoles via Michael reaction with hydrazine derivatives followed by cyclization strategy.^{3e,10} But to the best of our knowledge, the sulfur ylides derived from the Baylis–Hillman bromides have not been employed for [3 + 2] annulation reaction with appropriate dipolarophiles. It therefore occurred to us that sulfur ylides, derived from the Baylis–Hillman bromides (BH bromides), might in principle serve as a source of 1,3-dipoles

which can easily add to azodicarboxylates to provide the desired dihydropyrazole derivatives (retrosynthetic strategy is given in Scheme 1).

Scheme 1. Retrosynthetic Strategy for the Synthesis of Dihydropyrazole Derivatives **4**



Accordingly, we have first selected methyl (2Z)-2-bromomethyl-3-phenylprop-2-enoate (**1a**) as a source of 1,3-dipole for addition onto diethyl azodicarboxylate (DEAD) under the influence of Me₂S. In this direction the best results were obtained when we treated Baylis–Hillman bromide **1a** (1 mmol) with DEAD (**3a**) (1 mmol) in the presence of Me₂S (1.2 mmol) and K₂CO₃ (1 mmol) in acetonitrile/water (1 mL: 0.1 mL) solvent system at room temperature for 7 h to provide the expected dihydropyrazole derivative **4a** in 74% isolated yield. It is interesting to note that use of 0.1 mL of water is necessary (Table 1, entry 4) probably, to dissolve the in situ generated salt, thus making the reaction medium homogeneous leading to faster reaction rate with higher yields. To determine the generality of this methodology we have successfully transformed the various Baylis–Hillman bromides (**1a–i**) into dihydropyrazole derivatives (**4a–r**)¹¹ in 64–79% isolated yields via the simple one-pot reaction with diethyl and diisopropyl azodicarboxylates (Table 2, entries 1–18).

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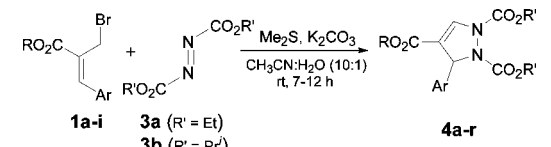
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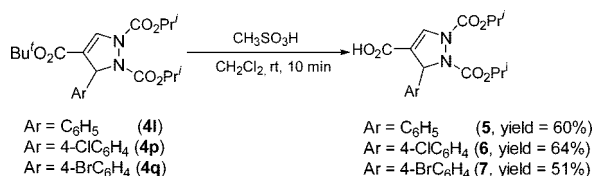
Table 2. Synthesis of Dihydropyrazole Derivatives **4a–r** via the Reaction of **1a–i** with DEAD (**3a**) and DIAD (**3b**)^a



entry	Ar	R	bromides	R'	t (h)	product ^b	yield ^c (%)
1	C ₆ H ₅	Me	1a	Et	7	4a	74
2	C ₆ H ₅	Et	1b	Et	8	4b	69
3	C ₆ H ₅	Bu ^t	1c	Et	9	4c	68
4	4-MeC ₆ H ₄	Me	1d	Et	8	4d	74
5	4-BrC ₆ H ₄	Me	1e	Et	10	4e	75
6	4-BrC ₆ H ₄	Bu	1f	Et	12	4f	66
7	4-ClC ₆ H ₄	Bu ^t	1g	Et	9	4g	67
8	4-BrC ₆ H ₄	Bu ^t	1h	Et	9	4h	64
9	3-ClC ₆ H ₄	Me	1i	Et	7	4i	69
10	C ₆ H ₅	Me	1a	Pr ⁱ	8	4j	75
11	C ₆ H ₅	Et	1b	Pr ⁱ	8	4k	67
12	C ₆ H ₅	Bu ^t	1c	Pr ⁱ	9	4l	69
13	4-MeC ₆ H ₄	Me	1d	Pr ⁱ	10	4m	79
14	4-BrC ₆ H ₄	Me	1e	Pr ⁱ	9	4n	75
15	4-BrC ₆ H ₄	Bu	1f	Pr ⁱ	12	4o	71
16	4-ClC ₆ H ₄	Bu ^t	1g	Pr ⁱ	9	4p ^d	67
17	4-BrC ₆ H ₄	Bu ^t	1h	Pr ⁱ	9	4q	74
18	3-ClC ₆ H ₄	Me	1i	Pr ⁱ	7	4r	70

^a All of the reactions were carried out on a 1 mmol scale of BH bromides (**1a–i**) with 1 mmol of dialkyl azodicarboxylates (**3a**, **3b**) in the presence of Me₂S (1.2 mmol) and K₂CO₃ (1 mmol) in CH₃CN (1 mL):H₂O (0.1 mL) at room temperature. ^b All of the compounds were isolated as colorless viscous liquids and fully characterized (see the Supporting Information). ^c Isolated yields were based on the BH bromides (**1a–i**). ^d On standing (for about 20–25 days), this compound became solid (mp 110 °C).

Scheme 2. Synthesis of Dihydropyrazole-4-Carboxylic Acids **5–7**^a

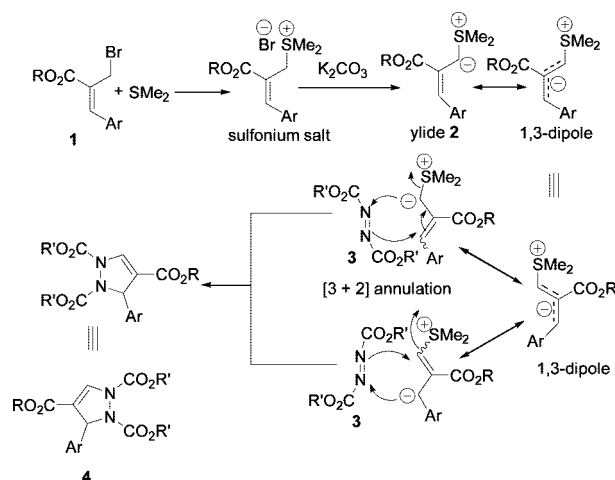


^a All reactions were carried out on a 0.5 mmol scale of **4l**, **4p**, and **4q** in the presence of CH₃SO₃H (1.5 mmol) in dichloromethane (1 mL).

To confirm further the structures of dihydropyrazole derivatives (**4a–r**) we have treated three representative esters **4l**, **4p**, and **4q** with CH₃SO₃H to obtain the corresponding acids **5–7** respectively as crystalline solids (Scheme 2). Single crystal X-ray data¹² of these acids (**5**, **6**, and **7**) are in complete agreement with the structures (see the Supporting Information for the ORTEP diagrams of **5**, **6**, and **7**).

A plausible mechanism for this interesting [3 + 2] annulation strategy is provided in Scheme 3. The reaction is believed to proceed first through the formation of sulfonium

Scheme 3. Plausible Mechanism



salt, via the reaction of Baylis–Hillman bromide (**1**) with dimethyl sulfide. This salt would become a ylide (**2**) in the presence of a base (K₂CO₃) and then serve as a 1,3-dipole (or an equivalent) for [3 + 2] annulation reaction with dialkyl azodicarboxylate (**3**) to provide the desired functionalized dihydropyrazole derivative **4**.

In conclusion, we have developed a novel [3 + 2] annulation strategy for the synthesis of an interesting class of pyrazole derivatives, with different substitution profiles, employing the Baylis–Hillman bromides as a valuable source of 1,3 dipoles in reaction with dialkyl azodicarboxylates in an operationally simple one-pot procedure.

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Supporting Information Available: Experimental procedures (with all spectral data, crystal data and ORTEP diagrams), ¹H and ¹³C NMR spectra of all compounds **4a–r**, **5**, **6**, and **7**; DEPT 135, NMR spectra for compounds **4d** and **4e**, CIF files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) One of the reviewers has asked the following question: Why does the double bond favor the spot out of conjugation between the aryl and the ester? We feel that this is probably due to the fact that the removal of proton (α to the aryl group) by base followed by double bond shift is not favorable due to electronic factors or this might be due to the fact that such kind of conjugation might result in steric crowding rendering the compound less stable.

(12) Detailed X-ray crystallographic data is available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, for compounds **5** (CCDC No. 678381), **6** (CCDC No. 678382), and **7** (CCDC No. 678383).