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A new approach to the synthesis of 3,4-dihydroisocoumarin derivatives

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ABSTRACT

A new, simple, one-step synthesis of 3-substituted 3,4-dihydroisocoumarins is developed. The products are obtained by the reaction of *o*-methoxycarbonyl arenediazonium bromides with unsaturated compounds in the presence of CuBr as a catalyst.

Isocoumarin and 3,4-dihydroisocoumarin derivatives are well-known compounds isolated from a wide variety of natural sources, and which exhibit a broad range of biological properties[1,2] such as antifungal,[3] antiallergic, antimicrobial,[4] immunomodulatory,[5] antitumour and/or cytotoxic,[6] anti-inflammatory,[7] plant growth inhibition[8] and enzyme inhibitory[9] activity. Isocoumarin derivatives are important precursors in the synthesis of many naturally occurring isoquinoline alkaloids and their analogues.[10]

A number of methods have been described for the synthesis of isocoumarins. The most common synthetic approach involves cyclization of homophthalic or 2-methylbenzoic acid derivatives.[11] While these transformations are widely used, they suffer from several notable disadvantages such as (i) the starting materials are often commercially unavailable, (ii) the reaction conditions are difficult to control and (iii) all the reagents must be of a high purity grade.

Another important method for the construction of the isocoumarin ring involves Sonogashira coupling followed by cyclization of alkynes containing a carboxylate or other substituent in proximity to the triple bond (Scheme 1).[12]

A number of isocoumarins have been prepared in good yields via Pd-catalyzed annulation of internal alkynes.[13] However, this method is somewhat limited in synthetic scope since it is highly selective for symmetrical disubstituted acetylenes. Furthermore, 2-iodobenzoic acid reacts with allene derivatives under palladium catalysis to afford the corresponding isocoumarins.[14]

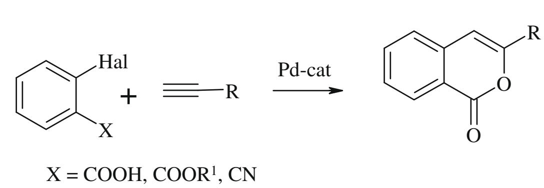
The purpose of our work was to study the syntheses of 3,4-dihydroisocoumarins via the Meerwein arylation reaction. Various approaches to the synthesis of benzoheterocycles from diazonium salts have been investigated. Intramolecular cyclization occurred in the reaction of unsaturated compounds with arenediazonium salts, which contained a suitable substituent *ortho-* to the diazonium group.[15]

A two-step synthesis of 3-substituted 3,4-dihydroisocoumarins based on the Meerwein arylation reaction was reported earlier.[16,17] 3-Cyano-3,4-dihydroisocoumarin was synthesized by the reaction of sodium with 2-(2-chloro-2-cyanoethyl)benzoic acid, which was obtained by the $CuCl_2$-mediated Meerwein arylation of acrylonitrile with 2-carboxybenzenediazonium chloride.[16]

Herein, we report a one-pot synthesis of 3,4-dihydroisocoumarin derivatives **3a–h** via the CuBr-catalyzed reaction of *o*-methoxycarbonyl benzenediazonium bromides **1a–d** with unsaturated compounds **2a–d** (Table 1). The key step involves intramolecular cyclization to give compounds **3a–h**. The reactions occurred under mild conditions in water–polar organic solvent medium [water–acetone (1:2) was found to be the best]. *o*-Ethoxycarbonyl benzenediazonium bromides were also converted into 3,4-dihydroisocoumarins **3a–h** in a similar manner to **1a–d**.[18]

In order to investigate the scope of this reaction, *o*-methoxycarbonyl benzenediazonium chloride **4** was reacted with methyl acrylate, ethyl acrylate and acrylonitrile. In this case, the usual Meerwein arylation products **5a–c** were obtained (Scheme 2 and Table 2, entries 1–3), and no cyclic products were isolated. Moreover, CuCl and $FeCl_2$[19] were also used as catalysts in this reaction which proceeded in a similar manner to give compounds **5a–c**.[20]

o-Carboxybenzenediazonium bromide **6** was examined in the reactions with methyl and ethyl acrylates **2a**,**e**, however, no cyclization reaction was observed. Acids **7a**,**b** were obtained using CuBr as catalyst (Scheme 3 and Table 2, entries 4 and 5).[21]



Scheme 1. Construction of the isocoumarin ring.

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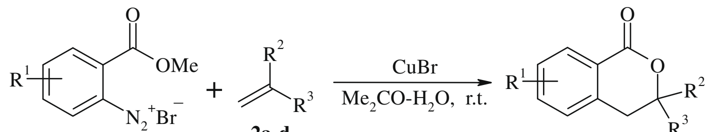
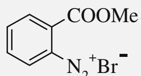
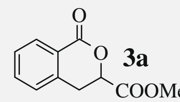
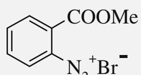
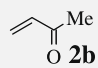
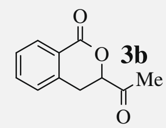
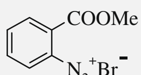
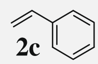
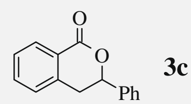
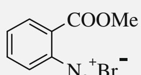
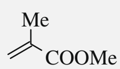
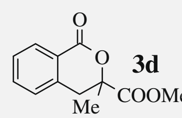
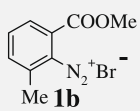
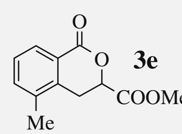
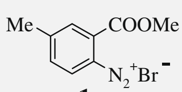
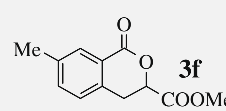
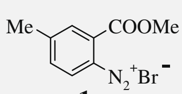
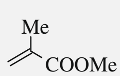
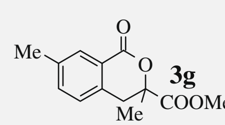
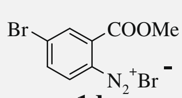
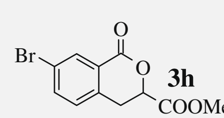
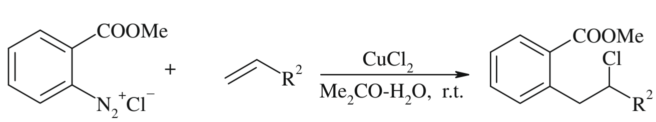
Table 1
Formation of 3,4-dihydroisocoumarins



1a-d 2a-d 3a-h

Entry	Diazonium salt	Olefin	Product	Yield[a] (%)
1	 1a	 2a	 3a	47
2	 1a	 2b	 3b	36
3	 1a	 2c	 3c	39
4	 1a	 2d	 3d	56
5	 1b	 2a	 3e	31
6	 1c	 2a	 3f	40
7	 1c	 2d	 3g	41
8	 1d	 2a	 3h	32

[a] Yield after purification.



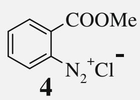
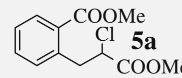
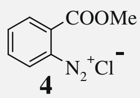
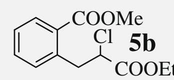
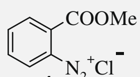
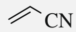
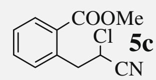
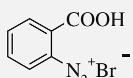
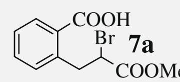
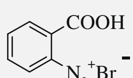
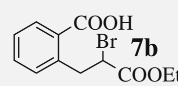
4 2a,e,f 5a-c

R^2 = COOMe (**a**); COOEt (**b**), CN (**c**)

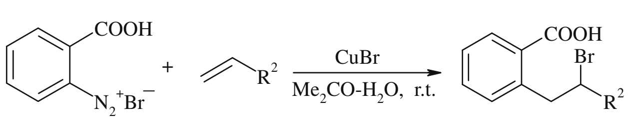
Scheme 2. Formation of the chloroarylation products. The reaction was carried out with **4** (obtained from 0.1 equiv of methyl anthranilate, HCl (40 mL) and 0.12 equiv of $NaNO_2$), 0.1 equiv of the corresponding olefin, acetone (100 mL), $CuCl_2$ (3.5 g), 0.5–1 h.

In summary, we have described a simple and efficient method for the preparation of 3,4-dihydroisocoumarin derivatives. Cyclization occurred to yield 3,4-dihydroisocoumarins **3**, when *o*-alkoxycarbonyl benzenediazonium bromides were used. In the case of *o*-carboxybenzenediazonium bromides and *o*-alkoxycarbonyl benzenediazonium chlorides, acyclic products were obtained. Further investigations on the scope and limitations of the reported method are in progress.

Table 2
Synthesis of arylation products **5a–c** and **7a**,**b**

Entry	Diazonium salt	Olefin	Catalyst	Product	Yield[a] (%)
1	 **4**	 **2a**	$CuCl_2$	 **5a**	45
2	 **4**	 **2e**	$CuCl_2$	 **5b**	35
3	 **4**	 **2f**	$CuCl_2$	 **5c**	40
4	 **6**	 **2a**	CuBr	 **7a**	36
5	 **6**	 **2e**	CuBr	 **7b**	30

[a] Yield after purification.



6 **2a,e** **7a,b**

R^2 = COOMe (**a**); COOEt (**b**)

Scheme 3. Formation of the bromoarylation products. The reaction was carried out with **6** (obtained from 0.1 equiv of anthranilic acid, HBr (40 mL, 48%) and 0.12 equiv of $NaNO_2$), 0.1 equiv of the corresponding olefin, acetone (100 mL), CuBr (3.5 g), 0.5–1 h.

Acknowledgement

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References and notes

1. Hill, R. A. *Forschr. Chem. Naturst.* **1986**, *49*, 1–78.
2. (a) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229–260; (b) Napolitano, E. *Org. Prep. Proced. Int.* **1997**, *29*, 631–664.
3. (a) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.; Nakajima, S. *Chem. Pharm. Bull.* **1981**, *29*, 2491–2495; (b) Meepagala, K. M.; Sturtz, G.; Wedge, D. E. *J. Agric. Food Chem.* **2002**, *50*, 6989–6992.
4. (a) Yoshikawa, M.; Harada, E.; Naitoh, Y.; Inoue, K.; Matsuda, H.; Shimoda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 2225–2230; (b) Matsuda, H.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **1999**, *7*, 1445–1450; (c) Hussain, M. T.; Rama, N. H.; Malik, A. *Indian J. Chem., Sect. B* **2001**, *40*, 372–376.
5. Matsuda, H.; Shimoda, H.; Yamahara, J.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 215–220.
6. (a) Whyte, A. C.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **1996**, *59*, 765–769; (b) Cai, Y.; Kleiner, H.; Johnston, D.; Dubowski, A.; Botic, S.; Ivie, W.; Di Giovanni, J. *Carcinogenesis* **1997**, *18*, 1521–1527; (c) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067–2081; (d) Cañedo, L. M.; Puentes, J. L. F.; Baz, J. P. *J. Antibiot.* **1997**, *50*, 175–176; (e) Sato, T.; Nagai, K.; Suzuki, K.; Morioka, M.; Saito, T.; Nohara, C.; Susaki, K.; Takebayashi, Y. *J. Antibiot.* **1992**, *45*, 1949–1952.
7. Furuta, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **1986**, *25*, 517–520.
8. Hashimoto, T.; Tori, M.; Asakawa, Y. *Phytochemistry* **1987**, *26*, 3323–3330.
9. Powers, J. C.; Asgian, J. L.; Ekici, Ö. D.; James, K. E. *Chem. Rev.* **2002**, *102*, 4639–4750.
10. (a) Houser, F. M.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 4676–4681; (b) Jones, J. B.; Pinder, A. R. *J. Chem. Soc.* **1958**, 2612–2618; (c) Tirodkar, R. B.; Usgaonkar, R. N. *Indian J. Chem.* **1972**, *10*, 1060–1064.
11. (a) Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835–3838; (b) Lewis, C. N.; Staunton, J.; Sunter, D. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 747–754; (c) Ohta, S.; Kamata, Y.; Inagaki, T.; Masuda, Y.; Yamamoto, S.; Yamashita, M.; Kawasaki, I. *Chem. Pharm. Bull.* **1993**, *41*, 1188–1190; (d) Izumi, T.; Morishita, N. *J. Heterocycl. Chem.* **1994**, *31*, 145–152; (e) Mehta, G.; Shah, S. R.; Venkateswarlu, Y. *Tetrahedron* **1994**, *50*, 11729–11742; (f) Rama, N. H.; Iqbal, R.; Zamani, K.; Saeed, A.; Iqbal, M. Z.; Choudhary, M. I. *Indian J. Chem., Sect. B* **1998**, *37*, 365–369; (g) Bovicelli, P.; Lupattelli, P.; Crescenzi, B.; Sanetti, A.; Bernini, R. *Tetrahedron* **1999**, *55*, 14719–14728; (h) Mal, D.; Bandyopadhyay, M.; Ghorai, S. K.; Datta, K. *Tetrahedron Lett.* **2000**, *41*, 3677–3680; (i) Hussain, M. T.; Rama, N. H.; Malik, A. *Indian J. Chem., Sect. B* **2001**, *40*, 372–376; (j) Yuan, H.; Junker, B.; Helquist, D.; Tailor, R. E. *Curr. Org. Synth.* **2004**, *1*, 1–9; (k) Donner, C. D.; Gill, M.; Tewierik, L. M. *Molecules* **2004**, *9*, 498–512.
12. (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922; (b) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778–4783; (c) Nakamura, Y.; Ukita, T. *Org. Lett.* **2002**, *4*, 2317–2320.
13. (a) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770–8779; (b) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271; (c) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713–5716; (d) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435–1442.
14. (a) Cherry, K.; Parrain, J.-L.; Thibonnet, J.; Duchêne, A.; Abarbri, M. *J. Org. Chem.* **2005**, *70*, 6669–6675; (b) Chakravarty, M.; Swamy, K. C. K. *J. Org. Chem.* **2006**, *71*, 9128–9138.
15. (a) Saunders, K. H.; Allen, R. L. M. *Aromatic Diazo Compounds*; Edward Arnold: London, 1985; (b) Zollinger, H. *Diazo Chemistry. I. Aromatic and Heteroaromatic Compounds*; VCH: Weinheim, 1994.
16. Malinowski, S. *Roczniki Chem.* **1952**, *26*, 85–97.
17. (a) Matiychuk, V. S.; Turytsya, V. V.; Obushak, N. D. *Chem. Heterocycl. Compd.* **2007**, *43*, 1589–1590; (b) Heinrich, M. R.; Wetzel, A.; Kirschstein, M. *Org. Lett.* **2007**, *9*, 3833–3835.
18. *Typical procedure for the arylation reaction*: A solution of sodium nitrite (8 g, 0.12 mol) in H_2O (15 mL) was added dropwise to a stirred and ice-cold mixture of methyl anthranilate (15.1 g, 0.1 mol, 12.9 mL), aqueous HBr (48%, 40 mL) and H_2O (40 mL) below 0–5 °C. The cold diazonium salt solution was slowly added to a vigorously stirred solution of CuBr (3.5 g) and olefin **2a–d** (0.1 mol)

in acetone (100 mL) at room temperature. The reaction was exothermic and the rate of addition was adjusted such that nitrogen gas was evolved at a rate of 2–3 bubbles/s (0.5–1 h). The resultant homogeneous solution was stirred for 30 min at 40 °C and then diluted with H_2O (150 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by distillation under reduced pressure to give isocoumarins **3a–h** as pale-yellow solids.

Methyl 1-oxo-3,4-dihydro-1H-isochromene-3-carboxylate **3a**: Yield 47%, bp 176–180 °C (1 mmHg), mp 83–84 °C (EtOH); ^{1}H NMR: (300 MHz, DMSO-d_6 + CCl_4): δ = 3.25 (dd, ^2J = 16.9 Hz, ^3J = 5.4 Hz, 1H), 3.49 (dd, ^2J = 16.9 Hz, ^3J = 5.7 Hz, 1H), 3.69 (s, 3H), 5.34 (t, J = 5.4 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H) 7.57–7.62 (m, 1H), 7.95 (d, J = 7.5 Hz 1H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ = 27.50, 53.34, 74.66, 125.12, 127.67, 127.98, 135.96, 136.38, 136.45, 164.10, 170.45; MS, m/z = 207 (M^++1); Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89. Found: C, 63.83; H, 4.72.

19. (a) Obushak, N. D. *Russ. J. Org. Chem.* **1999**, *35*, 309–310; (b) Obushak, N. D. *Russ. J. Gen. Chem.* **1998**, *68*, 443–445; (c) Ganushchak, N. I.; Obushak, N. D.; Polishchuk, O. P. *J. Org. Chem. USSR* **1982**, *18*, 633–639.

20. *Methyl 2-(2-chloro-2-cyanoethyl)benzoate* **5c**: Yield 40%, mp 61–62 °C (EtOH); ^{1}H NMR: (400 MHz, DMSO-d_6): δ = 3.73 (d, J = 7.6 Hz, 2H), 3.84 (s, 3H), 5.44 (t, J = 7.6 Hz, 1H), 7.48–7.51 (m, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ = 40.06, 43.89, 52.98, 118.30, 129.08, 130.09, 131.50, 133.33, 133.52, 136.30, 167.39; MS m/z = 224 (M^++1); Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.95; H, 4.60; N, 6.13.

21. *2-(2-Bromo-2-methoxycarbonylethyl)benzoic acid* **7a**: Yield 36%, mp 90–91 °C (EtOH); ^{1}H NMR: (300 MHz, DMSO-d_6): δ = 3.55 (dd, ^2J = 13.2 Hz ^3J = 7.2 Hz 1H), 3.65–3.75 (m, 4H), 4.63 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.41–7.47 (m, 1H), 7.96 (d, J = 7.5 Hz, 1H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ = 30.14, 46.51, 53.51, 128.26, 128.49, 128.65, 129.75, 134.66, 138.32, 164.12, 168.99; MS m/z = 287 (M^++1, ^{79}Br), 289 (M^++1, ^{81}Br); Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.02; H, 3.86; Br, 27.83. Found: C, 45.89; H, 3.69; Br, 27.60.

2-(2-Bromo-2-ethoxycarbonylethyl)benzoic acid **7b**: Yield 30%, mp 124–125 °C (EtOH); ^{1}H NMR: (400 MHz, DMSO-d_6 + CCl_4): δ = 1.17 (t, J = 7.6 Hz, 3H), 3.56 (dd, ^2J = 13.2 Hz, ^3J = 7.4 Hz, 1H), 3.67 (dd, ^2J = 13.2 Hz, ^3J = 7.8 Hz, 1H), 4.07–4.15 (m, 2H), 4.62 (t, J = 7.6 Hz, 1H), 7.28–7.50 (m, 3H), 7.94 (d, J = 7.8 Hz, 1H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ = 14.44, 30.14, 47.44, 61.87, 126.20, 127.35, 129.51, 132.25, 132.50, 136.30, 164.11, 168.07; MS m/z = 301 (M^++1, ^{79}Br), 303 (M^++1, ^{81}Br); Anal. Calcd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 47.80; H, 4.60.