A New Preparative Route to Substituted Carbazoles by Benzannulation

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Abstract: A new regioselective pathway to substituted carbazole derivatives is described here. According to this procedure substituted 2-alkoxycarbonyl-4-acetoxy-9-(*p*-toluenesulfonyl) carbazoles are obtained by treatment of substituted 6-[2-(*p*-toluenesulfonylamino)-aryl]-3-alkoxycarbonylhex-3-en-5-ynoic acids with acetic anhydride in the presence of sodium acetate. The latter acids are prepared from the easily available substituted *o*-iodo-anilines by Sonogashira coupling with propargylic alcohol and Wittig reaction as the key steps. The described benzannulation reaction proceeds in regiospecific fashion and a range of substituents are tolerated.

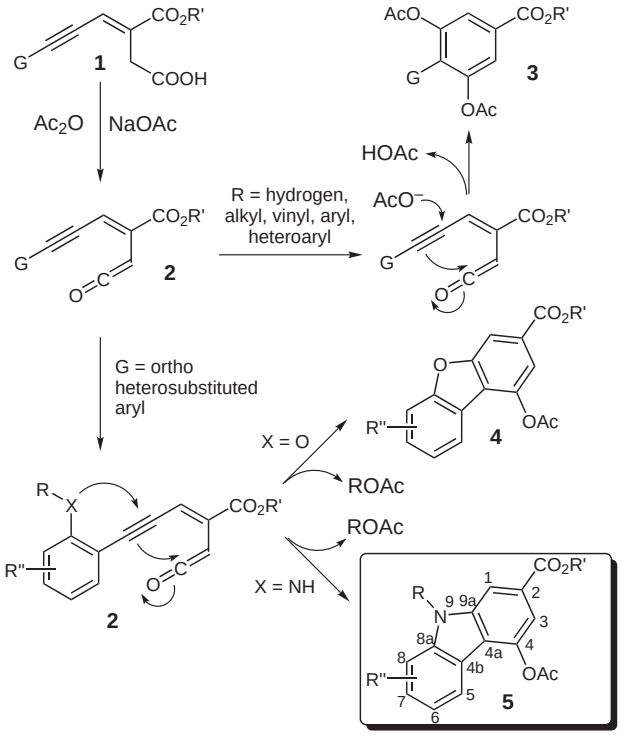
Key words: annulations, enynes, carbazoles, phenols, heterocycles

Carbazoles are relevant heteroaromatic compounds, which have attracted considerable attention because of their remarkable properties. Many natural alkaloids belong to this class and some of these display a wide range of biological activities.[1] Moreover, the photorefractive,[2] electrical,[3] light-emitting[4] and termal[5] properties of different carbazole derivatives have found several applications in the field of the sciences of the materials.

A large number of synthetic approaches to this kind of compounds have been established.[6] The conventional methodologies are based mainly on electrophilic substitution that takes place at the 3-, 6- and 9-position of the carbazole framework. For this reason the regioselective functionalization of the other positions still remains the major problem in carbazole synthesis.

Therefore, considerable effort has been devoted to the development of versatile and regioselective synthetic routes to carbazoles with functional groups at specific positions. The most recent applications are based on annulation reactions,[7] which allow the construction of carbazole nucleus by ring-formation approach.

We have previously developed the benzannulation reaction of the substituted 3,5-hexadienoic acids[8] to give the 4-substituted 3-hydroxy-benzoic acid derivatives. Recently, we described the annulation reaction of 3-alkoxycarbonylhex-3-en-5-ynoic acids[9] and of 6-(2-methoxyaryl)-3-alkoxycarbonylhex-3-en-5-ynoic acids[10] to give the 4-substituted 3,5-dihydroxybenzoic acid derivatives and the 1-acetoxy-3-alkoxycarbonyl dibenzofurans, respectively. We found that the treatment of the above-mentioned acids with acetic anhydride and sodium acetate affords the phenolic derivatives **3** and **4**, respectively (Scheme 1). The latter processes probably involves the ynenylketene **2**, formed from mixed anhydride of acid **1**, which may be cyclized through electrophilic attack and nucleophilic addition to the triple bond. If the substituent in position 6 of the ynoic acid shows the *o*-heteroaryl framework, the heteroatom could act as nucleophile to give addition to the triple bond. Both the heterocyclic ring and the phenolic ring are building up in the cyclization step to afford dibenzofurans **4** and carbazoles **5** depending of the heteroatom used. We herein report the new synthetic route to carbazole compounds **5** by benzannulation reaction of acids **1**.



Scheme 1 Proposed pathways to 4-substituted 3,5-diacetoxybenzoates, 1-acetoxy-3-alkoxycarbonyl dibenzofurans and 2-alkoxycarbonyl-4-acetoxy carbazoles.

An essential aspect of our approach is the specific preparation of the acids **1**. Preliminary studies focused on the selection of the protecting group on nitrogen atom. As mentioned above the heteroatom gives nucleophile addition to the triple bond providing that it will be unaffected by the activating agent (Ac_2O) used in the cyclization step. Moreover, the protecting group should be easily removed once the carbazole as be obtained. Therefore, few

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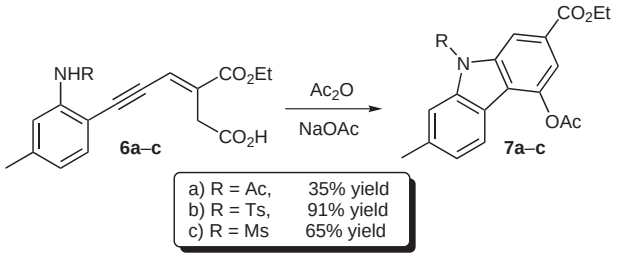
functional groups are suitable to this end. We choose the amidic linkage and then we tested the annulation reaction on acids **6a–c** (Scheme 2).

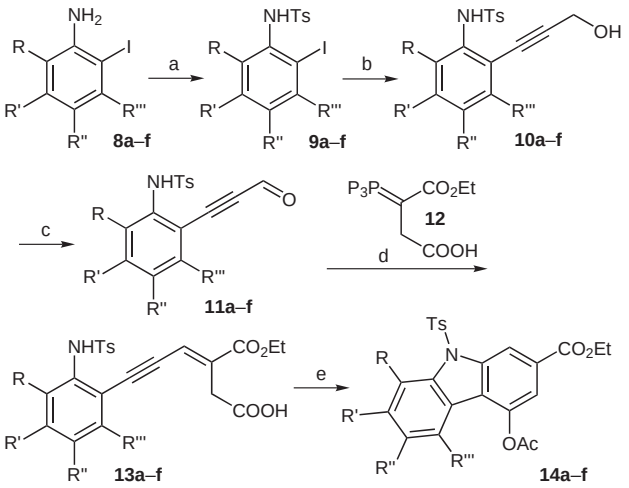


Scheme 2 *Reagents and conditions*: a) Ac_2O (30 equiv) and NaOAc (3 equiv), hydroquinone (0.05 equiv), then heating 3 h at reflux.

The results show that nitrogen on acetamide **6a** is not adequately nucleophile to obtain the cyclization product in good yields. Otherwise, the sulfonylamides **6b** and **6c** afforded the carbazoles **7b** and **7c** in good and moderate yields, respectively.

In all the described experiments the annulation do not proceeded further if the reaction time was prolonged. In forcing condition, only additional tar material was obtained.

In agreement with the latter optimization study and in consideration that *N*-sulfonycarbazoles are easily desulfonylated,[7p,11] we settled on the tosylamide derivatives to be employed in our synthetic route. The suitable substituted 6-[2-(*p*-toluenesulfonylamino)-aryl]-3-ethoxycarbonylhex-3-en-5-ynoic acids were prepared in four steps from the easily available substituted *o*-iodoanilines[12] **8a–f** (Scheme 3).



Scheme 3 *Reagents and conditions*: a) TsCl (1.2 equiv), pyridine; b) propargyl alcohol (2 equiv), Et_3N (3 equiv), CuI (0.01 equiv), $(Ph_3P)_2PdCl_2$ (0.01 equiv); c) MnO_2, CH_2Cl_2, 8 h at r.t.; d) **11a–f** and **12**, toluene–$CHCl_3$, r.t., 2 d; e) Ac_2O (10 equiv) and NaOAc (2 equiv), hydroquinone (0.05 equiv), then heating 1 h at reflux.

N-Tosylation of the aniline functionality was carried out with tosyl chloride and pyridine to give the substituted sulfonylamides **9a–f**. Sonogashira coupling[13] between **9a–f** and propargylic alcohol afforded alcohols **10a–f**, which were smoothly oxidized with MnO_2 to the corresponding aldehydes **11a–f** in quantitative yields. The subsequent Wittig reaction[14] with triphenyl-(α-ethoxycarbonyl-β-carboxyethyl)phosphonium ylide **12**[15] gave regioselectively[16] the suitable 6-[2-(*p*-toluenesulfonylamino)-aryl]-3-ethoxycarbonylhex-3-en-5-ynoic acids **13a–f** in yields ranging from 73% to 89% (Table 1).

The conversion of **13a–f** into benzannulated carbazoles was established by treatment[17] of the latter acids with an excess of acetic anhydride (10 equiv) in presence of sodium acetate (2 equiv) and hydroquinone (0.05 equiv) heating at reflux for one hour. The 2-ethoxycarbonyl-4-acetoxy-9-(*p*-toluenesulfonyl) carbazoles **14a–f** were obtained regioselectively in good yields (77–91%).

Speculation on the substitution pattern of the aromatic ring of the acids **13a–f** suggests some relevant considerations. Both position and quality of the substituents does not alter the reaction course. Moreover, this synthetic method proves to be very flexible since alkyl-, alkoxy-, carboxyalkyl-, halo-, and nitro groups were unaffected under the reaction conditions.

In conclusion, we have developed a new preparative method to substituted 2-alkoxycarbonyl-4-acetoxy carbazoles starting from substituted *o*-iodoanilines. Both the heterocyclic ring and one aromatic ring are formed in a single annulation step. Our approach is regiospecific, efficient and experimentally simple. Moreover, the starting materials are easily available or can be easily made. This route show some advantages over the classical processes as demonstrated by the synthesis of several new substituted carbazoles. Further application of this methodology for the preparation of the natural highly functionalized carbazoles and drug-related targets are underway.

Acknowledgment

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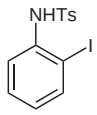
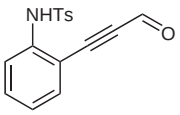
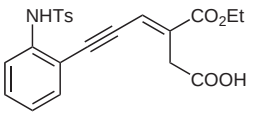
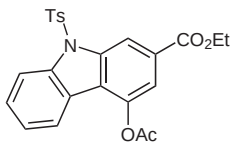
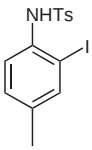
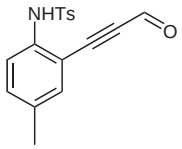
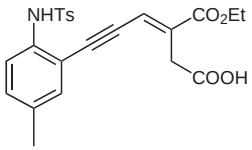
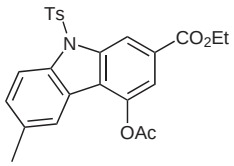
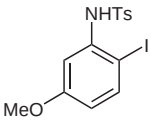
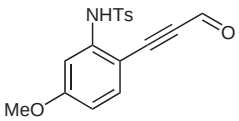
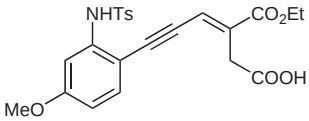
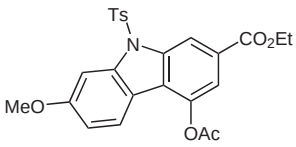
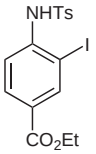
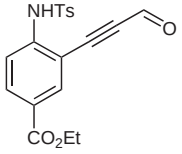
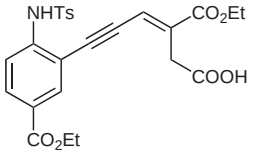
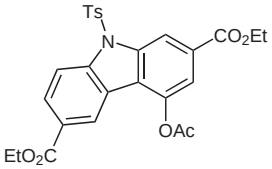
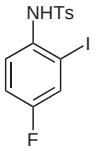
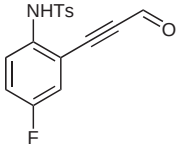
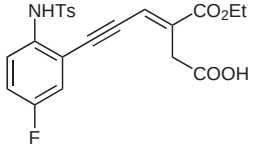
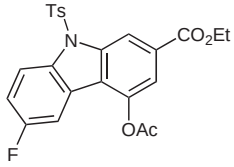
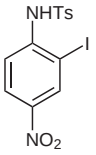
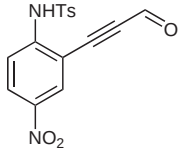
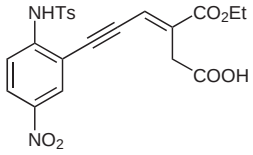
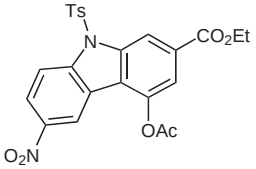
Table 1 Synthesis of Aldehydes **11**, Acids **13** and Carbazoles **14** from *o*-Iodoamides **9** (Scheme 3)

Entry	*o*-Iodoamides **9**	Aldehydes **11**	Coupling/ Oxidation (yields, %)	Acids **13**	Wittig (yields, %)[a]	Carbazoles **14**	Annulation (yields, %)[a]
a			93		87		89
b			94		89		90
c			90		84		82
d			92		82		87
e			93		89		91
f			86		73		77

[a] After chromatography and/or crystallization.

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(12) (a) 2-Iodoaniline **8a** is commercially available. The substituted 2-iodoanilines **8b**, **8c** and **8e** were prepared from the commercially available 4-methylaniline, 2-nitro-4-methoxyaniline and 4-fluoroaniline, respectively, according to the procedure described by Ma et al.[12b] Ethyl 4-amino-3-iodobenzoate **8d** and 4-nitro-2-iodoaniline **8f** were prepared from commercially available ethyl 4-aminobenzoate and 4-nitroaniline, respectively by iodination according to the procedure described by Spivey et al. and Adimurthy et al., respectively.[12c,d] (b) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*,

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(13) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) The coupling reaction was performed in THF solution using 2 equiv of propargyl alcohol, Et_3N as base and an equimolar amount of copper and palladium catalysts (0.01 equiv). Iododerivatives **9d** and **9f** show low solubility in THF and a mixture of THF–DMF was used as solvent.

(14) The Wittig reaction between aldehydes **11a**–**f** and ylide **12** was performed in toluene–$CHCl_3$ solution. The amount of $CHCl_3$ was adjusted depending on the solubility of the starting aldehydes. The above-mentioned reaction proceeds slowly at r.t. (typically 2 d). Notably, worse results have been obtained by heating the reaction mixture.

(15) For the preparation of this ylide see: Hudson, R. F.; Chopard, P. A. *Helv. Chim. Acta* **1963**, *46*, 2178.

(16) (a) Only *E*-isomers of acids **13** were obtained (NMR analysis). The Wittig reaction of ylide **12** with the aldehydes affords the 3-(*E*)-alkylidene-succinic acid monoalkyl esters in a highly stereoselective way; for previous studies on this reaction see: Paquette, L. A.; Schulze, M. M.; Bolin, D. *J. Org. Chem.* **1994**, *59*, 2043. (b) Röder, E.; Krauss, H. *Liebigs Ann. Chem.* **1992**, 177.

(17) Acids **13a**–**f** (50 mmol) were dissolved in acetic anhydride (48 mL, 0.5 mol). To this solution, anhyd NaOAc (8.2 g, 0.1 mol) and hydroquinone (275 mg, 2.5 mmol) were added in one portion. The obtained heterogeneous mixture was heated at reflux for 1 h under a nitrogen atmosphere. After cooling to r.t., the acetic anhydride was removed in vacuo and the residue was treated with EtOAc (300 mL) and H_2O (100 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography and crystallization to give carbazoles derivatives **14a**–**f**.

All new compounds were fully characterized. Selected analytical data:

Compound **13e**: Anal. Calcd for $C_{22}H_{20}FNO_6S$: C, 59.32; H, 4.53. Found: C, 59.45; H, 4.55. Mp 154 °C. FT-IR (nujol): 670, 954, 1030, 1100, 1189, 1280, 1363, 1448, 1466, 1539, 1594, 1633, 1697 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.40 (3 H, t, *J* = 7.2 Hz), 2.31 (3 H, s), 3.54 (2 H, s), 4.36 (2 H, q, *J* = 7.2 Hz), 6.75 (1 H, s), 7.06–7.20 (2 H, m), 7.16 (2 H, d, *J* = 8.3 Hz), 7.58 (2 H, d, *J* = 8.3 Hz), 8.18 (1 H, q, *J* = 4.4 Hz), 8.27 (1 H, s), 11.25 (1 H, br s). MS (EI): *m/z* = 446 [M^+ + 1], 445 [M^+], 290, 262, 246, 216, 200, 172, 155, 91, 65.

Compound **14e**: Anal. Calcd for $C_{24}H_{20}FNO_6S$: C, 61.40; H, 4.29. Found: C, 61.50; H, 4.30. Mp 197–198 °C (hexane–$CHCl_3$). FT-IR (nujol): 666, 861, 1027, 1087, 1175, 1207, 1299, 1369, 1417, 1472, 1591, 1722, 1763 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.46 (3 H, t, *J* = 7.2 Hz), 2.27 (3 H, s), 2.49 (3 H, s), 4.47 (2 H, q, *J* = 7.2 Hz), 7.13 (2 H, d, *J* = 8.3 Hz), 7.27 (1 H, dt, *J* = 9.0, 2.5 Hz), 7.54 (1 H, dd, *J* = 8.2, 2.5 Hz), 7.69 (2 H, d, *J* = 8.3 Hz), 7.85 (1 H, s), 8.31 (1 H, dd, *J* = 9.0, 4.3 Hz), 8.86 (1 H, s). MS (EI): *m/z* = 470 [M^+ + 1], 469 [M^+], 427, 382, 354, 334, 315, 290, 272, 244, 227, 200, 171, 155, 139, 120, 91, 65.