

NUCLEOPHILIC DISPLACEMENT OF ACTIVATED ARYL TRIFLATES
A NEW SYNTHESIS OF OXINDOLES AND ARYLACETIC ACIDS

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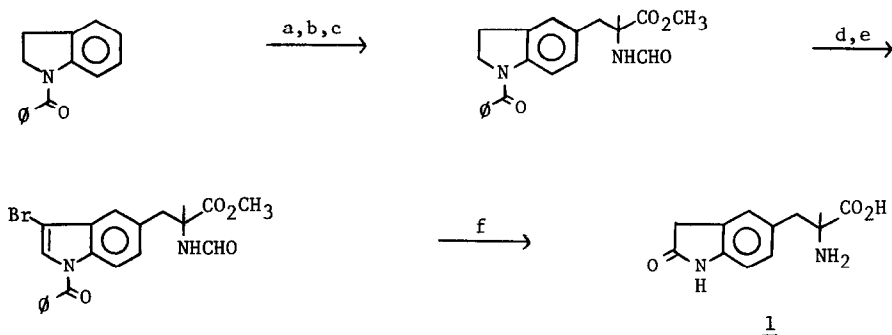
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Summary: 2-Nitroaryl triflates undergo efficient base-catalyzed nucleophilic displacement by dimethyl malonate anion to yield dimethyl nitroarylmalonates, which subsequently are converted in high yields to nitroarylacetic acids and oxindoles.

During the course of a program on the synthesis of a series of arylalanine derivatives related to the antihypertensive agent α -methyldopa¹, we required the synthesis of the oxindoles 1 and 2. Our first synthesis of 1, as shown in Scheme 1, gave a very low overall yield due primarily to a poor conversion in the last step and to difficulties in isolation. In an effort to develop an improved synthesis of 1 and 2, we have discovered a new synthesis of nitroarylacetic acids and oxindoles, which is the subject of the present communication.

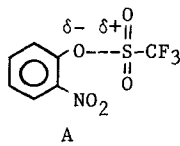
Scheme 1



- a) $\text{CH}_2\text{O}/\text{HCl}/\text{HOAc}$ (80%); b) $\text{CH}_3\text{CH}(\text{NC})\text{CO}_2\text{CH}_3/\text{CH}_3\text{ONa}$ (75%); c) HCl/EtOAc (76%);
d) DDQ (75%); e) $\text{Br}_2/\text{CHCl}_3$ (92%); f) $\text{HCl}/\text{MeOH}/\text{H}_2\text{O}$ (10%)

The ready availability of 3-hydroxy-4-nitrobenzyl chloride (3)² led us to investigate the possibility of nucleophilic displacement of a sulfonate ester of the nitrophenol moiety by a species such as malonate anion through an addition-elimination mechanism. However, it is well known that nucleophilic reactions of nitrophenyl sulfonates give rise to considerable, and at

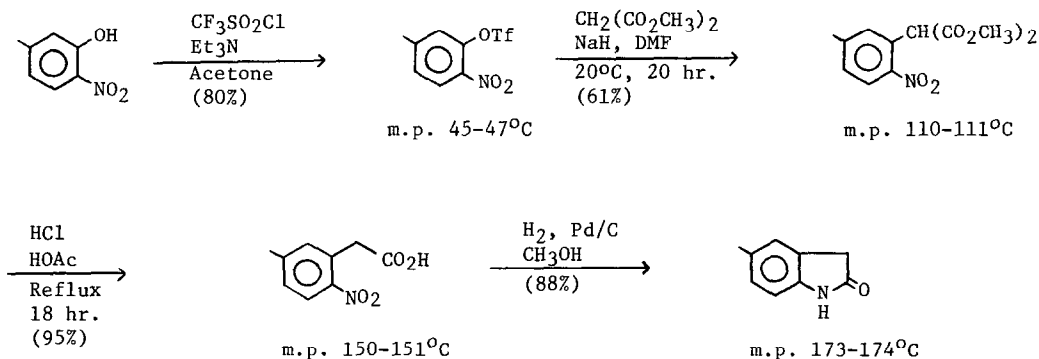
times almost exclusive S-O cleavage with regeneration of the nitrophenol³. However, we reasoned that the corresponding triflate esters might be less prone to undergo S-O cleavage than the tosylates. Thus, the possible transition state A for S-O cleavage with a partial positive charge on the sulfur atom would, we considered, be less stable than the corresponding transition state for tosylates or mesylates, due to the strongly electron-withdrawing -CF₃ group. Thus we hoped that the balance would be tipped to favor nucleophilic attack at the aromatic carbon⁴.



The above expectation has now been realized and we have found that nitroaryl triflates can be displaced efficiently with malonate anion to yield the corresponding nitrophenylmalonates, from which the synthesis of oxindoles is straightforward.

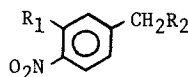
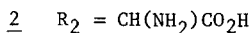
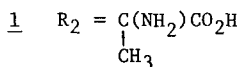
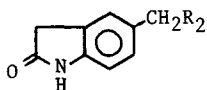
The reaction sequence is exemplified with the synthesis of the model compound, 5-methyl-oxindole (Scheme 2).

Scheme 2



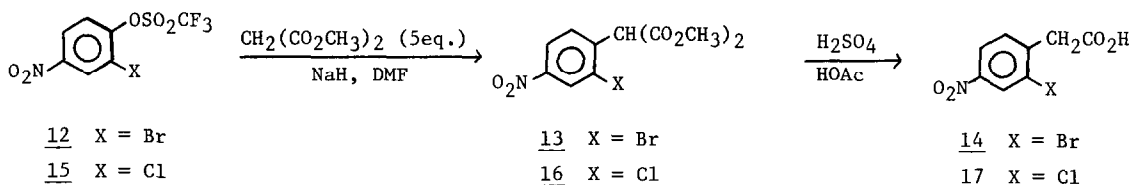
Alkylation of ethyl acetamidocyanoacetate or methyl 2-isocyanopropionate with 3, followed by mild acid hydrolysis, led to nitrophenols 4⁵ (56%, m.p. 159-161°C) and 5 (73%, m.p. 113-115°C), respectively. Reaction with trifluoromethanesulfonyl chloride (acetone, Et₃N, reflux 2 hr.) then yielded the triflate esters 6 (84%, m.p. 127-129°C) and 7 (96%, m.p. 109-111°C). Reaction of the nitrotriflates with dimethyl malonate (20% excess) in refluxing acetonitrile containing five equivalents of anhydrous K₂CO₃ for 24 hr. gave the nitroaryl malonates 8 (65%, oil) and 9 (67%, m.p. 155-156°C). Refluxing of the blocked derivatives in 8N HCl for 3 hr. produced the nitroarylacetic acids 10 (m.p. 239°C, dec.) and 11 (m.p. 215-217°C) in over 90% yield. Finally, reduction of 10 and 11 with SnCl₂ in HCl gave rise to the desired oxindoles 2 (65%, m.p. 295-300°C, dec., isolated as the hydrochloride hydrate) and 1 (59%, m.p. 330-335°C, dec., isolated as the monohydrate), respectively.

In this way, 1 was prepared in 25% overall yield as compared to 3% by the route outlined in Scheme 1.



<u>3</u>	HO	Cl
<u>4</u>	HO	C(CN)(NHAc)CO ₂ Et
<u>5</u>	HO	C(CH ₃)(NHCHO)CO ₂ Me
<u>6</u>	CF ₃ SO ₂ O-	C(CN)(NHAc)CO ₂ Et
<u>7</u>	CF ₃ SO ₂ O-	C(CH ₃)(NHCHO)CO ₂ Me
<u>8</u>	CH(CO ₂ Me) ₂	C(CN)(NHAc)CO ₂ Et
<u>9</u>	CH(CO ₂ Me) ₂	C(CH ₃)(NHCHO)CO ₂ Me
<u>10</u>	CH ₂ CO ₂ H	CH(NH ₂)CO ₂ H
<u>11</u>	CH ₂ CO ₂ H	C(CH ₃)(NH ₂)CO ₂ H

In a preliminary investigation of the generality of this triflate displacement⁶ we have investigated the reaction of the two representative para-nitrophenyl triflates 12 and 15 because of an independent interest in the arylacetic acids 14 and 17. The triflates were converted to the malonates 13⁷ (m.p. 105.5-107.5°C) and 16 (m.p. 111-112.5°C) in 78% and 83% yield, respectively, which were then hydrolyzed to 14⁷ (m.p. 163-165°C) and 17 (m.p. 159-160°C) in near quantitative yields.



The triflate displacement described here serves as an excellent complement to the well known displacement of halonitrobenzenes⁸ in that many ortho- and para-nitrophenols are readily available by nitration of the corresponding phenol. In addition to a new synthesis of oxindoles⁹ as described herein, the triflate displacement constitutes a new and practical synthesis of nitroarylacetic acids since the malonate intermediates can be decarboxylated in near quantitative yields. Some nitrophenylacetic acids are available by nitration of the phenylacetic acids, but nitration of ortho-chlorophenylacetic acid, for example, gives rise to 2-chloro-5-nitrophenylacetic acid rather than 17¹⁰, and reaction of nitrobenzylhalides with cyanide often gives low yields of nitrophenylacetoneitriles due to base catalyzed side reactions of the reactive CH₂ group¹¹.

The scope and limitations of the triflate displacement¹² as well as the extension of this work to other activating groups and anions continues under active investigation.

Acknowledgements

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References and Notes

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2. S. B. Hanna, Y. Iskander and A. Salama, J. Chem. Soc., 221 (1961).
3. J. F. Bunnett and J. V. Bassett, Jr., J. Am. Chem. Soc., 81, 2104 (1959).
4. Dr. R. A. Firestone (Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey) has suggested that the difference of behavior between the nitroaryl tosylates and nitroaryl triflates may be due to the powerful rate retarding effect of the α -CF₃ group on nucleophilic attack at the sulfur atom. Cf. F. G. Bordwell and W. T. Brannen, Jr., J. Am. Chem. Soc., 86, 4645 (1964). Further discussion of the mechanistic aspects of the triflate displacement is deferred for a full publication.
5. All new compounds had satisfactory analytical results and spectral data.
6. Generally, the triflates are formed easily at room temperature without need of heating. The malonate displacement proceeds at room temperature over a period of 16 hr. using NaH in DMF; using K₂CO₃ in acetonitrile at reflux, the reaction requires 24 hr. Yields by the two methods appear to be comparable.
7. This experiment was carried out by Drs. J. Rokach and R. Lapalme.
8. Cf. R. L. Augustine, A. J. Gustavsen, S. F. Wanat, I. C. Pattison, K. S. Houghton and G. Koletar, J. Org. Chem., 38, 3004 (1973).
9. Recent syntheses of oxindoles: (a) P. G. Gassman and T. J. van Bergen, J. Am. Chem. Soc., 96, 5508 (1974); (b) A. G. Schultz and W. K. Hagmann, J. Org. Chem., 43, 4231 (1978).
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