Pergamon

Tetrahedron Letters 43 (2002) 9175–9178

TETRAHEDRON LETTERS

A direct synthesis of 2-arylpropenoic acid esters having nitro groups in the aromatic ring: a short synthesis of (±)-coerulescine and (±)-horsfiline†

N. Selvakumar,* A. Malar Azhagan, D. Srinivas and G. Gopi Krishna

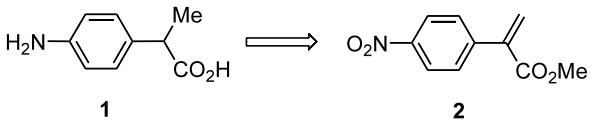
Department of Discovery Chemistry, Discovery Research, Dr. Reddy's Laboratories Ltd., Miyapur, Hyderabad 500 050, India

Received 14 August 2002; revised 23 September 2002; accepted 4 October 2002

Abstract—A short synthesis of 2-arylpropenoic acid esters that possess nitro groups in their phenyl ring using common and less expensive reagents is described. The usefulness of this methodology is substantiated by the efficient total syntheses of (±)-coerulescine and (±)-horsfiline from the 2-arylpropenoic acid esters obtained.

2-Arylpropenoic acids signify a medicinally important class of non-steroidal anti-inflammatory agents.[1] 2-Arylpropenoic acids possessing nitro groups in their aromatic rings such as **2** are potential starting materials for the preparation of several analgesic and anti-inflammatory 2-(4-aminophenyl)propionic acid derivatives of type **1** (Fig. 1).[2] In addition, these compounds have served as potential intermediates in certain natural product syntheses[3,4] and other purposes.[5] There have been a few reports concerning the syntheses of this class of compounds. While the procedure of Cho et al. started with *p*-nitroacetophenone,[6] the other two procedures warranted *p*-nitrophenylacetic acids as starting materials.[7,8] Furthermore, the first procedure involves reaction of dichlorocarbene in a two-phase system using a phase-transfer catalyst and is not commonly followed in the literature. The classical procedure that is frequently used in the preparation of these compounds involves reacting the appropriate phenylacetic acid ester with ethyl oxalate under basic conditions followed by treating the resultant oxalo-ester with aq. formaldehyde in the presence of K_2CO_3.[7] The third procedure involved a Mannich reaction in converting *p*-nitrophenylacetic acid to the target compound.[8] Very recently, a palladium-catalyzed coupling of an α-stannyl acrylate to a nitro-aryl iodide has been disclosed as a method of preparing these compounds.[9] Herein, we report a direct and straightforward synthesis of the title compounds from readily available starting materials in two steps employing less expensive reagents.

Our synthesis started from commercially available aromatic nitro compounds having leaving groups in either the *ortho* or *para* position with respect to the nitro group. The aromatic nucleophilic substitution of dimethyl malonate onto 2-fluoronitrobenzene **3** afforded the nitro-malonate **4** as reported earlier from this laboratory (Scheme 1).[10] The treatment of nitro-malonate **4** with aq. formaldehyde in the presence of K_2CO_3 cleanly afforded the nitro-aryl propenoate **5**. This conversion was expected to occur with initial decarboxylation followed by the aldol condensation of the resultant aryl acetic acid derivative with formaldehyde in one-pot and this was eventually confirmed by carrying out the conversion in a stepwise manner. Thus, treatment of nitro-malonate **4** with aq. K_2CO_3 resulted in decarboxylation giving the nitro-phenyl acetate **6**, which underwent aldol condensation with formaldehyde leading to the nitro-aryl propenoate **5**.[11] This preparation of compound **5** from commercially available 2-fluoronitrobenzene in two steps constitutes a short synthesis of a 2-arylpropenoic acid ester possessing a nitro group in the aromatic ring.



1 2

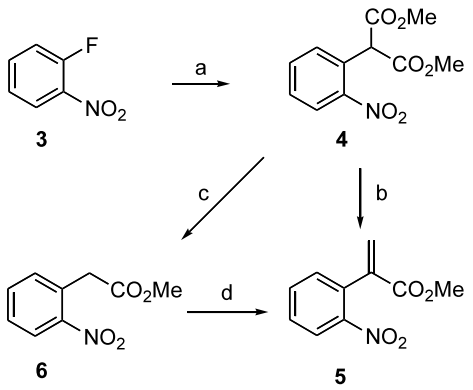
Figure 1.

Keywords: 2-arylpropenoic acid; anti-inflammatory agents; aromatic nucleophilic substitution; aldol condensation; oxindole alkaloids; 1,3-dipolar cycloaddition.

* Corresponding author. Tel.: 91-40-3045439; fax: 91-40-3045438; e-mail: selvakumarn@drreddys.com

† DRL Publication No. 234.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02267-0



Scheme 1. *Reagents and conditions*: (a) NaH, dimethyl malonate, THF, rt, 83%; (b) K_2CO_3, formalin, 60°C, 75%; (c) K_2CO_3, H_2O, 60°C, 70%; (d) K_2CO_3, formalin, 60°C, 62%.

Having obtained a 2-arylpropenoic acid ester possessing a nitro group in the aromatic ring in two steps from commercial materials, we turned our attention to generalize the protocol and the results are summarized in Table 1. A wide variety of aromatic nitro compounds possessing functional groups ranging from halogens such as chlorine (entries 2 and 3) and fluorine (entries 5 and 6) to methyl (entry 7) and trifluoromethyl groups (entry 8) were chosen as starting materials for the study. While the first step of aromatic nucleophilic substitution occurred in excellent yields in almost all the systems, the second step had varied yields from moderate to very good. The diversity with which the 2-arylpropenoic acid esters could be prepared as shown in Table 1 reveals the potential of this method in the synthesis of this type of compound.

Table 1. Examples of the preparation of 2-arylpropenoic acid esters

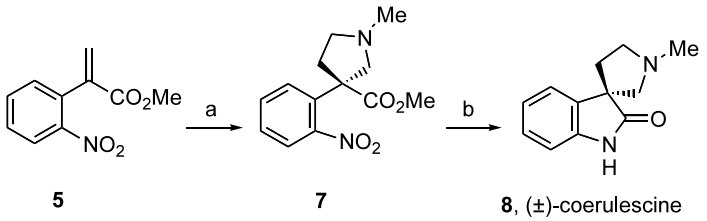
Entry	Starting material	Yield of compound analogous to	
		4 (%)	**5** (%)
1	1-Chloro-2,4-dinitrobenzene	89	59
2	3,4-Dichloronitrobenzene	85[a]	70
3	1,2,3-Trichloro-5-nitrobenzene	80	48
4	1-Fluoro-4-nitrobenzene	88[a]	33[b]
5	3,4-Difluoronitrobenzene	89	32[b]
6	3,4,5-Trifluoronitrobenzene	83	24[b]
7	3-Fluoro-4-nitrotoluene	62	52
8	2-Chloro-3,5-dinitrobenzotrifluoride	86	41

[a] Reported from this laboratory before.[10]
[b] The poor yield is due to the formation of a Michael addition product (ca. 25%).[12]

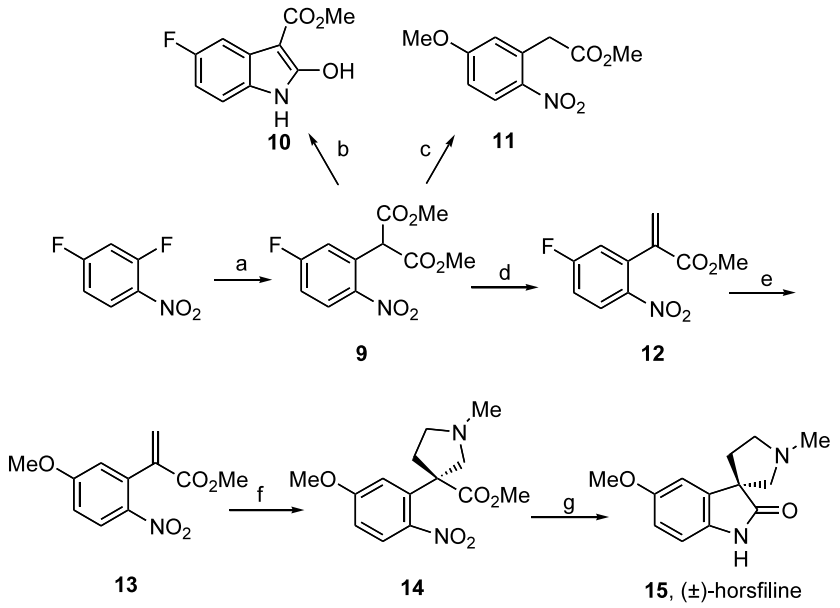
In addition to the anticipated use of these compounds in preparing analogues of anti-inflammatory compounds, we have also used them as starting materials for the synthesis of oxindole alkaloids in a bid to substantiate the potential of these compounds in organic synthesis. (−)-Horsfiline **15** was the first alkaloid isolated in 1991, among other known alkaloids, from a Malaysian medicinal tree *Horsfieldia superba* Warb. belonging to the *Horsfieldia* genus by Bodo and co-workers.[13] Recently, Colegate and co-workers isolated a related oxindole alkaloid (−)-coerulescine **8** from *Phalaris coerulescens*.[14] Horsfiline had attracted wide attention from synthetic chemists and many methodologies were applied to its synthesis.[15] We report the syntheses of both the natural alkaloids in their racemic form from the 2-arylpropenoic acid esters obtained using the above methodology.

The 2-arylpropenoic acid ester **5** obtained in two steps from 2-fluoronitrobenzene was converted to (±)-coerulescine **8** in two further steps using the route reported byPalmisano and co-workers.[15a] Thus, the 1,3-dipolar cycloaddition of the nitro-ester **5** to a *N*-methylazomethine ylide, generated from *N*-methylglycine and paraformaldehyde, afforded smoothly the pyrrolidine nitro-ester **7** in very good yield (Scheme 2). Subsequent hydrogenation of the compound resulted in clean cyclization leading to (±)-coerulescine **8** in only two steps from the nitro-ester **5** obtained using our method. Thus, the synthesis of (±)-coerulescine was achieved in four steps from commercial material with an overall yield of 45%.

Analogously, the synthesis of (±)-horsfiline **15** warranted the synthesis of nitro-ester **13** possessing a methoxy group in the aromatic ring starting the synthesis from 2,4-difluoronitrobenzene (Scheme 3). Our initial plan was to introduce a methoxy group to the fourth position of 2,4-difluoronitrobenzene by a selective aromatic nucleophilic substitution but this procedure failed as the reaction occurred at both fluorine atoms resulting in 2,4-dimethoxynitrobenzene. Thus, we changed our strategy to introduce initially dimethyl malonate, though we expected both regioisomers, and



Scheme 2. Synthesis of (±)-coerulescine. *Reagents and conditions*: (a) Sarcosine, $(CH_2O)_n$, 3 Å molecular sieves, toluene, reflux 86%; (b) H_2, 10% Pd/C, MeOH, 84%.



Scheme 3. Synthesis of (±)-horsfiline. *Reagents and conditions*: (a) NaH, dimethyl malonate, THF, rt, 73%; (b) H_2, 10% Pd/C, MeOH, 62%; (c) NaH, MeOH, rt then 60°C, 51%; (d) K_2CO_3, formalin, 60°C, 80%; (e) NaH, MeOH, rt, 76%; (f) Sarcosine, $(CH_2O)_n$, 3 Å molecular sieves, toluene, reflux 66%; (g) H_2, 10% Pd/C, MeOH, 83%.

subsequently introduce the methoxy group to the *para* position of the 2-isomer. To this end, the treatment of dimethyl malonate with 2,4-difluoronitrobenzene and NaH was carried out and we obtained predominantly one isomer in good yield (the other isomer formed in less than 5%). We identified the major isomer as the required *ortho*-addition product **9** based on the similarity of its aromatic splitting pattern in the ^{1}H NMR spectrum with that of commercially available 2-nitro-4-fluorotoluene. The structure of **9** was unambiguously confirmed by hydrogenating to the oxindole compound **10**, which exists as the aromatic indole compound. Having obtained the required isomer **9**, we next turned our attention to introduce the methoxy group to the *para* position. Thus, treatment of nitro-diester **9** with NaOMe in methanol at rt resulted only in recovery of starting material. However, at 60°C substitution of the methoxy group to the fourth position occurred with concurrent decarboxylation yielding the unwanted nitro-ester **11**. Consequently, we planned to introduce the methoxy group after forming the 2-arylpropenoic acid ester moiety, which was accomplished under the usual conditions giving the nitro-acrylate **12**. Treatment of **12** with NaOMe in methanol cleanly gave the desired methoxy nitro-acrylate **13** in 76% yield.[15a,16] The further steps to complete the synthesis of (±)-horsfiline **15** were performed as usual. Thus, the synthesis of (±)-horsfiline was achieved in five steps from a commercially available substance with an overall yield of 24%. The spectral data of synthetic (±)-coerulescine **8** and (±)-horsfiline **15** were comparable in all respects with those of literature values.[17]

In conclusion, we have developed a short and direct method for the preparation of 2-arylpropenoic acid esters possessing nitro groups in their phenyl rings. The synthesis involves commercially available starting materials and less expensive reagents than those previously reported. We believe that the methodology, which led to the accessibility of a wide range of nitro-acrylates, would be useful in the preparation of analogues of anti-inflammatory drugs. The potential of this method was substantiated by the short syntheses of the oxindole alkaloids (±)-coerulescine **8** and (±)-horsfiline **15** in excellent overall yields from commercially available starting materials and the syntheses should be amenable for the preparation of the natural products in large scale for biological evaluation.

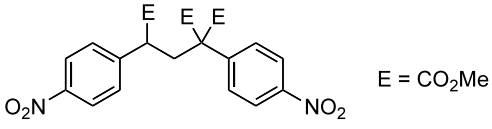
Acknowledgements

We thank Dr. K. Anji Reddy for his continued encouragement in this work. The help extended by Dr. R. Rajagopalan and Dr. Sanjay Trehan is greatly acknowledged. We appreciate the services rendered by the Analytical Research Department of Discovery Research, Dr. Reddy's Laboratories for this communication.

References

1. Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1985**, *41*, 4095.
2. Dumaitre, B.; Fouquet, A.; Perrin, C.; Cornu, P. J.; Boucherle, A.; Plotka, C.; Domage, G.; Streichenverger, G. *Eur. J. Med. Chem.-Chim. Ther.* **1979**, *14*, 207 (CA: **1979**, *91*, 157398n).
3. Jefford, C. W.; Zaslona, A. *Tetrahedron Lett.* **1985**, *26*, 6035.
4. Jefford, C. W.; Kubota, T.; Zaslona, A. *Helv. Chim. Acta* **1986**, *69*, 2048.

5. Schauble, J. H.; Freed, E. H.; Swerdloff, M. D. *J. Org. Chem.* **1971**, *36*, 1302.
6. Cho, Y. S.; Yeo, J. H. *Soul Taehakkyo Yakhak Nonmunjip* **1984**, *9*, 37 (CA: **1986**, *104*, 186092a).
7. (a) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180; (b) Schinz, H.; Hinder, M. *Helv. Chim. Acta* **1947**, *30*, 1349; (c) Ames, G. R.; Davey, W. *J. Chem. Soc.* **1958**, 1794.
8. Schauble, J. H.; Hertz, E. *J. Org. Chem.* **1970**, *35*, 2529.
9. Levin, J. I. *Tetrahedron Lett.* **1993**, *34*, 6211.
10. Selvakumar, N.; Reddy, B. Y.; Kumar, G. S.; Iqbal, J. *Tetrahedron Lett.* **2001**, *42*, 8395.
11. Procedure for the preparation of compound **5** from nitro-diester **4**: To a mixture of nitro-diester **4** (2 g, 7.9 mmol) in formalin (37–41%, 15 mL) was added a solution of K_2CO_3 (1.63 g, 11.85 mmol) in water (5 mL). The resultant mixture was heated to 60°C for 2 h and then cooled to rt. The reaction mixture was added to water and extracted with ether (4×50 mL). The combined organic extracts were washed with brine and dried. The residue obtained upon evaporation of the volatiles was purified on a column of silica gel to afford the nitro-acrylate **5** as a colorless oil (1.2 g, 75%). IR (neat, ν cm^{-1}): 1728, 1528, 1351, 1210; δ_H (200 MHz, $CDCl_3$): 8.15 (d, $J=8.3$ Hz, 1H), 7.68–7.52 (m, 2H), 7.42 (d, $J=7.3$ Hz, 1H), 6.57 (s, 1H), 5.91 (s, 1H), 3.75 (s, 3H); mass (CI method): 208 (M^++1), 176.
12. We have observed some quantities of adducts in these cases corresponding to the following structure, which are formed by the Michael addition of compounds analogous to **4** onto the 2-arylpropenoic acid esters **5**.



13. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.
14. (a) Anderton, N.; Cockrum, A. P.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Willing, R. I. *Phytochemistry* **1998**, *48*, 437; (b) Somei, M.; Noguchi, K.; Yamagami, R.; Kawada, Y.; Yamada, K.; Yamada, F. *Heterocycles* **2000**, *53*, 7; (c) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705.
15. (a) Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447; (b) Lizos, D.; Tripoli, R.; Murphy, J. A. *Chem. Commun.* **2001**, *1*, 2732; (c) Kumar, U. K. S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193; (d) Bascop, S.-I.; Sapi, J.; Laronze, J.-Y.; Levy, J. *Heterocycles* **1994**, *38*, 725; (e) Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979.
16. The methoxy-acrylate **13** was used by Palmisano et al. as an intermediate in the synthesis of (–)-horsfiline. However, their ^{13}C NMR had an extra peak at δ 114.0. Thus, we completed the synthesis of (±)-horsfiline **15** along the lines reported by them to confirm our structure **13**. Data of compound **13**: mp 109°C; IR (KBr, ν cm^{-1}): 1710, 1512, 1322, 1254; δ_H (200 MHz, $CDCl_3$): 8.19 (d, $J=9.1$ Hz, 1H), 6.96 (dd, $J=9.1$, 2.7 Hz, 1H), 6.83 (d, $J=2.7$ Hz, 1H), 6.51 (s, 1H), 5.83 (s, 1H), 3.92 (s, 3H), 3.74 (s, 3H); δ_C (50 MHz, $CDCl_3$): 165.12, 163.38, 140.42, 140.17, 133.45, 127.0, 126.57, 117.25, 113.40, 55.83, 52.00; mass (CI method): 238 (M^++1), 206.
17. Spectral data of synthetic (±)-coerulescine **8** (lit.[14a]): mp 110°C; IR (neat, ν cm^{-1}): 3210, 1710, 1619, 1471; δ_H (200 MHz, $CDCl_3$): 8.57 (br s, 1H), 7.40 (d, $J=7.3$ Hz, 1H), 7.20 (t, $J=7.5$ Hz, 1H), 7.04 (t, $J=7.3$ Hz, 1H), 6.90 (d, $J=7.8$ Hz, 1H), 2.89 (s, 2H), 3.10–2.70 (m, 2H), 2.47 (s, 3H), 2.50–2.00 (m, 2H); δ_C (50 MHz, $CDCl_3$): 183.30, 140.48, 135.73, 127.47, 122.79, 122.35, 109.60, 65.77, 56.40, 53.50, 41.51, 37.59; mass (CI method): 203 (M^++1). Spectral data of synthetic (±)-horsfiline **15** (lit.[13]): mp 153°C; IR (neat, ν cm^{-1}): 1707, 1488, 1206, 1032; δ_H (400 MHz, $CDCl_3$): 8.35 (br s, 1H), 7.07 (d, $J=2.4$ Hz, 1H), 6.80 (d, $J=8.6$ Hz, 1H), 6.73 (dd, $J=8.6$, 2.4 Hz, 1H), 3.81 (s, 3H), 3.11–3.06 (m, 1H), 2.96–2.79 (m, 3H), 2.51 (s, 3H), 2.46–2.09 (m, 2H); δ_C (50 MHz, $CDCl_3$): 183.14, 156.00, 135.03, 133.76, 112.48, 110.06 (2C), 65.77, 56.51, 55.70, 54.08, 41.58, 37.85; mass (CI method): 233 (M^++1).