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A direct entry to the 1-methoxyindole skeleton and to the corresponding indoles by a novel rearrangement: general syntheses of substituted 1-methoxyindoles☆

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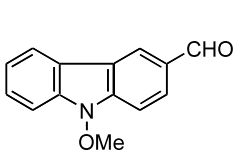
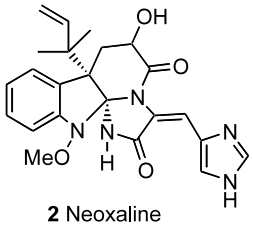
Abstract—A short and efficient route to 1-methoxyindoles via a novel rearrangement is disclosed. This route involves only three steps from commercially available nitro compounds. The methodology is also generalized with a variety of examples to afford a series of 2-substituted-1-methoxyindoles possessing an electron-withdrawing group at position 3. In addition, a 1-methoxyindole compound **10** was converted to the corresponding indole **11** under mild conditions thereby constituting a new synthesis of substituted indoles.

Alkaloids possessing the 1-methoxyindole structural framework are a group of biologically important natural products.[1] Representative examples possessing the 1-methoxyindole structural feature include, among many others, 9-methoxycarbazole-3-carbaldehyde **1** isolated from *Murraya euchrestifolia* HAYATA (Rutaceae) and 4,9-dimethoxy-1-vinyl-β-carboline isolated from *Picrasma quassioides*, the latter compound is a powerful inhibitor of cAMP phosphodiesterase.[2,3] In addition, neoxaline **2**, isolated from *Aspergillus japonicus* Fg-551, is a complex tetracyclic alkaloid having an *N*-methoxyindoline based structure, which was found to stimulate the central nervous system.[4] Furthermore, the biological significance of alkaloids possessing an indole structure is well documented.[5] However, the biological properties of compounds possessing the 1-methoxyindole skeleton have not been extensively explored due to the difficulty in the synthesis of the 1-methoxyindole ring in comparison to the corresponding indoles and special procedures or reagents are required for their synthesis.[1] Among the three methods in the literature to construct this framework, the first protocol of Acheson and co-workers involves multiple steps and is not generally applicable to the synthesis of 1-methoxyindoles.[6] While the second method of Somei and co-workers suffers from the drawback of employing expensive reagents such as *N*,*N*-dimethylformamide dimethylacetal,[7] the third procedure, also by the same group, requires an existing indoline ring in order to achieve the preparation of 1-methoxyindoles.[8] In an ongoing program on the synthesis and evaluation of biological values of alkaloids possessing the 1-methoxyindole skeleton, an efficient synthesis was sought to prepare multigram quantities in order to undertake structure activity relationship studies. To this end, herein we disclose a direct synthesis of 1-methoxyindoles in three steps from readily available aromatic compounds involving a novel rearrangement.



1 9-Methoxycarbazole -3-carbaldehyde



2 Neoxaline

Our synthetic route to 1-methoxyindoles involves a novel rearrangement of a nitro-diester of type **5** where E represents a carbomethoxy group (Scheme 1). The preparation of compounds of type **5** was accomplished using our reported procedure for the double alkylation method of dimethyl malonate.[9] Nitro-diesters of type **5** undergo a novel rearrangement upon treatment with NaCl in DMSO at high temperatures affording methoxyindoles of type **6**.

Keywords: rearrangement; alkaloid; alkylation; decarboxylation; nucleophilic catalysis.

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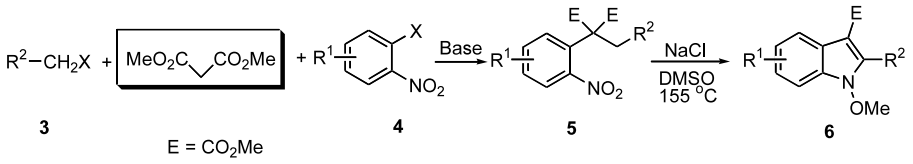
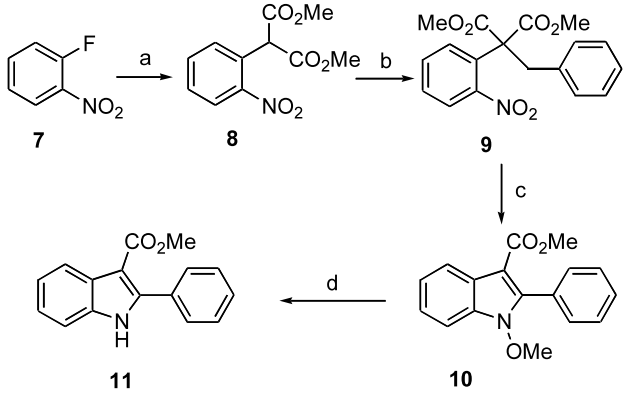


Scheme 1.

Alkylation of the nitro-diester **8**, obtained from dimethyl malonate and 2-fluoronitrobenzene, with benzyl bromide under basic conditions gave compound **9** in very good yield (Scheme 2). The alkylated nitro-diester **9**, when added to a solution of NaCl in DMSO at 155°C, underwent rearrangement resulting in the 1-methoxyindole **10**.[10] The structure of **10** was deduced based on spectral data and additional evidence was derived by converting **10** into the known compound **11** by hydrogenolysis.[11] The melting point and spectral data of the synthetic methyl 2-phenylindole-3-carboxylate **11** matched with the literature data in all aspects. This procedure constitutes the shortest (three steps) synthesis of the 1-methoxyindole skeleton reported to date. In addition, the overall process also constitutes a new synthesis of 2-substituted indoles.

We believe that the new rearrangement follows a nucleophilic catalysis mechanism based on the results of the following parallel experiments. The formation of methoxyindole compound **10** was complete in 30 min at 155°C when two experiments were performed on the nitro-diester **9** with 3 and 0.2 equiv. of NaCl in DMSO indicating that only a catalytic amount of chloride is required as reported in the decarboxylation of malonates.[12] Further evidence was drawn for the predicted nucleophilic catalysis mechanism from the experiment where nitro-diester **9** was heated without NaCl in neat DMSO to the same temperature which resulted only in the recovery of starting material.

Having achieved a novel route to the methoxyindole structural framework, we turned our attention to generalize the methodology. A summary of the 1-methoxy-2-



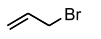
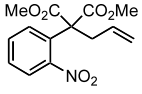
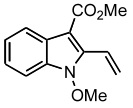
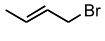
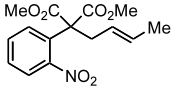
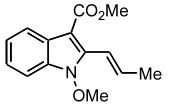
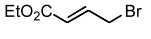
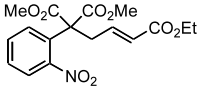
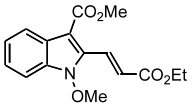
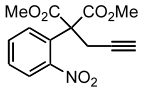
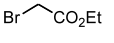
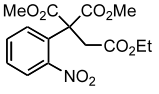
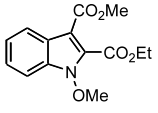
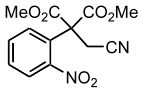
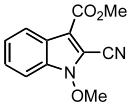
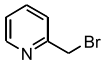
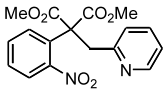
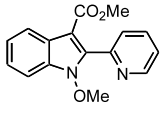
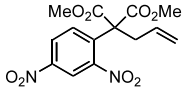
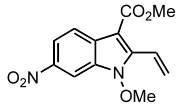
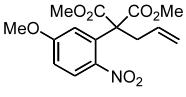
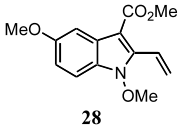
Scheme 2. *Reagents and conditions*: (a) dimethyl malonate, NaH, THF, 0→60°C, 75%; (b) NaH, DMF, $PhCH_2Br$, rt, 72%; (c) NaCl, DMSO, 155°C, 85%; (d) H_2, 10% Pd/C, MeOH, 90%.

substituted indole compounds[14] synthesized by this method is presented in Table 1. The choice of alkyl halides to arrive at substrates for the rearrangement is flexible as substrates derived from allyl halides (entries 1 and 2, Table 1) and an allyl halide possessing an electron withdrawing functionality (entry 3, Table 1) underwent a similar rearrangement to afford the corresponding methoxyindoles **13**, **15** and **17** respectively in good yields. However, the substrate **18**, derived from propargyl bromide, neither underwent rearrangement nor decarboxylation. The starting materials **19** and **21**, prepared from halides possessing α-electron withdrawing groups, also afforded rearrangement products **20** and **22** in similar yields. It is interesting to note that the novel rearrangement is also feasible on substrate **23**, derived from a heterocyclic halide such as 2-bromomethylpyridine, as it provided the rearranged compound **24** thereby paving the way to make a variety of 2-heterocyclyl-1-methoxyindoles for biological studies (entry 7, Table 1). In an effort to further generalize this protocol for different aromatic rings, the substrate **25**, derived from 1-chloro-2,4-dinitrobenzene using our usual procedure, was subjected to the rearrangement conditions resulting in methoxyindole **26** possessing a substituted aromatic ring. The substituted aromatic compound **27** afforded the rearranged compound **28** along similar lines. This study clearly established the feasibility of the novel rearrangement on a wide variety of substrates rendering access to various 2-substituted-1-methoxyindoles.

In conclusion, we have developed a novel methodology for the preparation of the 1-methoxyindole skeleton in the shortest number of steps reported to date. Using this methodology, a number of 2-substituted-1-methoxyindoles could be prepared which is otherwise a difficult task using the hitherto reported methods. The preparation of methoxyindole compound **24** possessing a heterocyclic moiety deserves special mention. The preparation of the compounds of type **5** and **6**, in principle, should be amenable for parallel synthesis considering the similarity and the simplicity of the reaction conditions thus paving the way to the synthesis of a large number of 2-substituted-1-methoxyindoles for biological evaluation. In addition, the synthetic protocol also constitutes a new synthesis of indoles as the methoxyindoles can be converted to the corresponding indoles under mild reaction conditions.

We believe that the simplicity with which the substituted methoxyindoles were prepared in this work could

Table 1. Examples of the preparation of various 2-substituted-1-methoxyindoles possessing methoxycarbonyl at C-3

Entry	Alkyl halide	**Compounds Analogous to 5**	Yield	**Compounds Analogous to 6**	Yield[a]
1		 **12**	77%	 **13**	55%
2		 **14**	83%	 **15**	63%
3		 **16**	72%	 **17**	51%
4		 **18**	87%	No product[b]	0%
5		 **19**	94%	 **20**	60%
6		 **21**	77%[c]	 **22**	55%
7		 **23**	69%[c]	 **24**	60%
8		 **25**[d]	67%	 **26**[e]	70%
9		 **27**[f]	74%	 **28**	62%

[a] In a few cases, the corresponding decarboxylated product in yields ranging from 2 to 10% was observed.[10] [b] Only starting material was recovered. [c] Yield based on recovered starting material. [d] 1-Chloro-2,4-dinitrobenzene was used as the starting material for this substance. [e] The reaction for the preparation of this compound was performed at 120°C. [f] Prepared from 2,4-difluoronitrobenzene.[13]

trigger a new area of research among synthetic and medicinal chemists to unravel the biological properties of this group of alkaloids. The application of this methodology to prepare a variety of 1-methoxyindoles along with their corresponding indoles and their biological evaluation is under progress in our laboratory. The usefulness of this methodology is substantiated by a direct total synthesis of 9-methoxycarbazole-3-carbaldehyde **1** in the following letter.[15]

Acknowledgements

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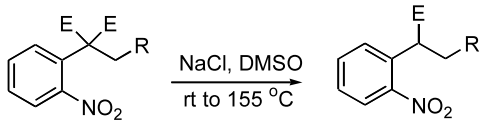
10. (a) It is important to note that the starting material should be added to a 155–160°C solution of NaCl in DMSO. In cases where we heated all the reactants together gradually from rt to 155°C, significant amounts of decarboxylated products were isolated.



(b) **Experimental procedure for 10**: A solution of the nitro-diester **9** (500 mg, 1.5 mmol) in DMSO (10 mL) was added using a syringe pump to a preheated (155°C, oil bath temperature) and stirred solution of NaCl (255 mg, 4.4 mmol) in DMSO (10 mL) over 15 min. The resultant mixture was further stirred for 30 min and then allowed to cool to ambient temperature. The reaction mixture was worked-up by adding water followed by extraction with ethyl acetate. The combined organic extracts were washed with water, brine and dried. The residue obtained upon evaporation of the solvent was passed through a column of silica gel to afford compound **10** (300 mg, 75%) as a colorless oil, which became solid upon storage in a refrigerator. Further elution yielded the mono-decarboxylated product (ca. 10%) as an oil. An analytical sample of compound **10** was obtained by washing the solid with dry hexane. Mp 80–82°C; IR (neat, ν cm^{-1}): 1699, 760; δ_H (400 MHz, $CDCl_3$): 8.26–8.23 (m, 1H), 7.67–7.29 (m, 8H), 3.79 (s, 3H), 3.72 (s, 3H); δ_C (50 MHz, $CDCl_3$): 50.6, 64.8, 100.8, 108.3, 121.9, 122.4, 122.8, 123.3, 127.6 (2C), 128.3, 129.0, 130.5 (2C), 131.2, 141.3, 165.0. Mass (CI): 282 (M^++1), 250. Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.57; H, 5.38; N, 4.98; found: C, 72.37; H, 5.16; N, 5.25.

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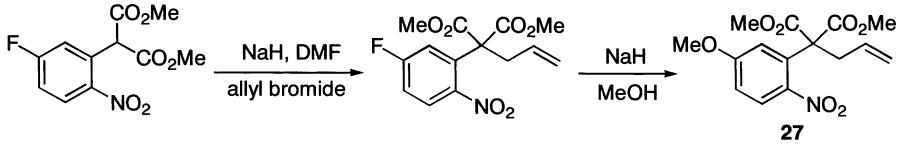
12. Kraphcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *14*, 957.
13. Compound **27** was prepared as follows. Also see: Selvakumar, N.; Azhagan, M. A.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175.



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14. Selected spectral data: **13**: IR (neat, ν cm^{-1}): 1697,1439, 1212, 1114; δ_H (200 MHz, $CDCl_3$): 8.15 (d, J=7.3 Hz, 1H), 7.69–7.26 (m, 4H), 6.40 (d, J=18.1 Hz, 1H), 5.75 (d, J=12.2 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H); δ_C (50 MHz, DMSO-d_6): 164.5, 136.2, 131.8, 124.1, 123.7, 122.4, 121.9, 121.8, 121.7, 108.5, 100.7, 64.5, 50.9. Mass (CI): 232 (M^++1), 200. **15**: IR (neat, ν cm^{-1}): 1700,1440; δ_H (200 MHz, $CDCl_3$): 8.12 (d, J=7.0 Hz, 1H), 7.43–7.23 (m, 4H), 7.03–6.91 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.06 (dd, J=6.7 and 1.6 Hz, 3H); δ_C (50 MHz, $CDCl_3$): 165.8, 137.7, 134.7, 132.0, 123.3, 122.5, 122.2, 121.9, 118.5, 107.9, 100.0, 63.8, 50.8, 20.0. Mass (CI): 246 (M^++1), 214.

17: Mp 112–114°C; IR (KBr, ν cm^{-1}): 1709, 1634, 1215; δ_H (200 MHz, $CDCl_3$): 8.56 (d, $J=16.6$ Hz, 1H), 8.21 (d, $J=8.3$ Hz, 1H), 7.50–7.27 (m, 3H), 7.03 (d, $J=16.6$ Hz, 1H), 4.33 (q, $J=7.3$ Hz, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 1.39 (t, $J=7.3$ Hz, 3H); δ_C (50 MHz, DMSO-d_6): 166.0, 164.2, 132.8, 132.6, 129.5, 125.6, 123.1, 122.6, 122.2, 121.7, 109.0, 104.2, 65.3, 60.6, 51.4, 14.1. Mass (CI): 304 (M^++1), 272, 258. Anal. calcd for $C_{16}H_{17}NO_5$: C, 63.34; H, 5.65; N, 4.62; found: C, 62.91; H, 5.88; N, 4.47. **26**: mp 144–146°C; IR (KBr, ν cm^{-1}): 1709, 1500, 1346; δ_H (200 MHz, $CDCl_3$): 8.38 (d, $J=1.7$ Hz, 1H), 8.27–8.10 (m, 2H), 6.60 (dd, $J=18.1$ and 12.2 Hz, 1H), 6.52 (d, $J=18.3$ Hz, 1H), 5.92 (d, $J=12.2$ Hz, 1H), 4.06 (s, 3H), 3.97 (s, 3H); δ_C (50 MHz, $CDCl_3$): 164.5, 144.3, 141.1, 130.9, 126.8, 124.4, 123.5, 122.5, 117.5, 104.9, 102.2, 65.0, 51.4. Mass (EI) 276 (M^+), 245, 199. **28**: IR (neat, ν cm^{-1}): 1696,1441, 1201; δ_H (200 MHz, $CDCl_3$): 7.64 (d, $J=2.4$ Hz, 1H), 7.56–7.26 (m, 2H), 6.97 (dd, $J=8.9$ and 2.4 Hz, 1H), 6.34 (d, $J=18.0$ Hz, 1H), 5.71 (d, $J=12.1$ Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H); δ_C (50 MHz, DMSO-d_6): 164.7, 155.9, 136.1, 126.9, 123.8, 122.8, 121.7, 114.2, 109.6, 103.4, 100.2, 64.7, 55.4, 51.0. Mass (CI): 262 (M^++1), 254.

15. Selvakumar, N.; Khera, M. K.; Reddy, B. Y.; Srinivas, D.; Azhagan, M. A.; Iqbal, J. *Tetrahedron Lett*. **2003**, *44*, 7071.