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From Simple Ugi Adducts to Indanes and δ-Amidomalonates: New Manganese(III)-Induced Radical Cascades

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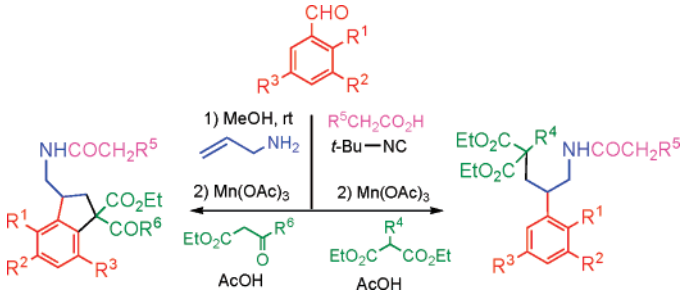
ABSTRACT



A complete change of the traditional Ugi adducts framework has been obtained using new radical cascades as Ugi post-condensation reactions. Indanes and δ-amidomalonates were thus obtained in a one-pot procedure from aromatic aldehydes under a sequence involving Ugi addition followed by treatment of the adducts with Mn(III) and malonate or β-ketoester. The radical step probably involves an intramolecular aryl transfer followed by an oxidative cleavage and final cyclization to indanes.

Since the pioneering work of Ugi, the use of isocyanides has been strongly associated with the multicomponent formation of peptide derivatives.[1] Most recent efforts on this reaction have focused on the extension of molecular diversity by the use of post-condensation reactions.[2] Cycloadditions,[3] cyclocondensations,[4] or organometallic couplings[5] with properly functionalized Ugi adducts have thus been thoroughly reported giving, in particular, access to many different cyclic scaffolds. Notwithstanding all these reports, the structural diversity reached by all these processes is often limited by the peptide nature of the adducts which is partially retained in the final compounds. Our contention was that radical cascades could further increase the potential of Ugi four-component reactions and give scaffolds of high diversity with structures contrasting with the traditional Ugi peptide backbone. The success encountered by the tin free radical procedure[6] coupled with the very few reports on the use of radical couplings on Ugi adducts[7] encouraged us further in this direction.

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(2) Marcaccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 2, pp 33−75.

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(5) (a) Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155−3158. (b) Krelaus, R.; Westermamann, B. *Tetrahedron Lett.* **2004**, *45*, 5987−5990. (c) Kazmaeir, U.; Hebach, C.; Watzke, A.; Maier, S.; Mues, H.; Huch, V. *Org. Biomol. Chem.* **2005**, *3*, 136−145. See also ref 2.

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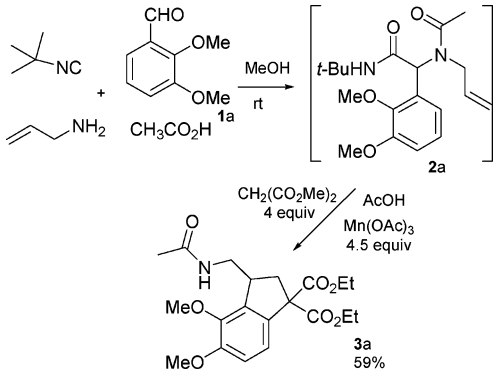
Following our initial study on the reactivity of xanthate-tethered Ugi adducts,[7] we turned our attention to the use of manganese acetate. The most interesting features of Mn(III)-based radical chemistry are the ability to easily form radicals from β-dicarbonyl compounds coupled with efficient intra- and intermolecular additions due to slow oxidation of electron-deficient radicals.[8] These properties have allowed the disclosure of efficient radical cascades by selecting the appropriate combination of allyl and aryl residues in the starting material.[9]

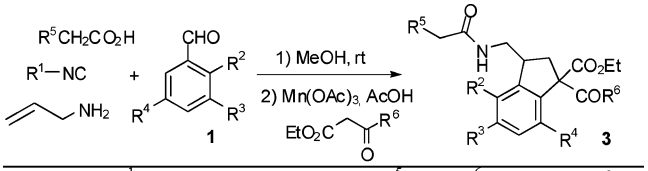
When equimolar amounts of 2,3-dimethoxybenzaldehyde, allylamine, *tert*-butylisocyanide, and acetic acid were added in MeOH, the Ugi adduct **1a** was formed in quantitative yield. Evaporation of the solvent, followed by treatment with diethylmalonate and manganese acetate in refluxing acetic acid, affords substituted indane **3a** (Scheme 1). This one-pot Ugi/Mn(III) oxidation sequence probably represents one of the most efficient formations of complex cyclopentanes from aldehyde derivatives.[10]

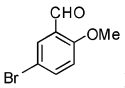
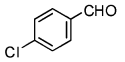
Scheme 1. Indane Formation from Aromatic Aldehydes



Various aldehydes (**1a**−**1e**) behaved similarly forming amidoindanes (**3a**−**3f**) in good to moderate yields (Table 1). As most of these Ugi adducts were formed in quantitative yields, the given yields basically represent the efficiency of the radical cascade.

Table 1. Indane Formation



Entr	R^1	Starting aldehyde	R^5	R^6	**3** (%)[a]
1	Cy	 **1a**	H	OMe	**3a** (52)
2	*t*-Bu	**1a**	"	Me	**3b** (60)[b]
3	"	 **1c**	"	OMe	**3c** (42)
4	"	 **1d**	"	"	**3d** (63)[c]
5	"	 **1e**	"	Me	**3e** (63)[d]
6	"	**1a**	Ph	OMe	**3f** (40)[c,e]
7	"	 **1f**	H	"	-
8	"	 **1g**	"	"	-

[a] Ugi reaction was performed with equimolar amount of reagents in molar methanol and left overnight at room temperature. The oxidation step was performed in acetic acid (90 °C, 0.3 M) with 4 equiv of malonate or ketoester and 4.5 equiv of manganese acetate; the reaction was stopped after decoloration of the medium (3−6 h). [b] Obtained as a 1:1.2 mixture of diastereomers. [c] Six equivalents of manganese was used instead of 4.5. [d] Obtained as a 1:1.5 mixture of diastereomers. [e] Overall isolated yield after purification of intermediate Ugi adduct.

In terms of diversity, the loss of the isocyanide part in the first step of the sequence is counterbalanced by the addition of the malonyl moiety in the second step, allowing the disclosure of a new four-component indane formation. Indeed, the malonyl group can be efficiently replaced by other activated methylene derivatives: ethylacetoacetate behaves similarly in this reaction, giving the new indanes **3b** and **3e** as a mixture of diastereomers with low diastereoselectivity (entries 2 and 5). Other amide derivatives may be formed as well by the proper choice of the starting carboxylic acid. With phenylacetic acid (entry 6), the Ugi adduct formation was not however quantitative (60%); the intermediate was best purified before the oxidation final step to give **3f** in a 69% isolated yield.

The reaction sequence seems to need an ortho substituent on the aromatic aldehyde: though *p*-chlorobenzaldehyde

(6) For some recent papers on tin free radical reactions, see: (a) Kim, S.; Lim, C. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3265−3267. (b) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345−4348. (c) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645−1648. (d) Schaffner, A.-P.; Renaud, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2658−2660. (e) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267−273.

(7) El Kaim, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259−8261.

(8) For reviews on manganese(III) acetate reactions, see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−364. (b) Melikyan, G. G. In *Organic Reactions*; Paquette, L., Ed.; John Wiley: New York, 1997; Vol. 49, Chapter 3, p 427. For recent examples of Mn(III)-based radical reactions, see: (c) Yang, D.; Ye, X. Y.; Xu, M.; Pang, K. W.; Cheung, K. K. *J. Am. Chem. Soc.* **2000**, *122*, 1658−1663. (d) Zhang, Z.; Wang, G. W.; Miao, C. B.; Dong, Y. W.; Shen, Y. B. *Chem. Commun.* **2004**, 1832−1833. (e) Chen, Z. X.; Wang, G. W. *J. Org. Chem.* **2005**, *70*, 2380−2383. (f) Fu, W.-J.; Huang, X. *J. Organomet. Chem.* **2007**, *692*, 740−745. (g) Tanyeli, C. Ozdemirhan, D. *Tetrahedron* **2005**, *61*, 8212−8217.

(9) For some radical cascades induced by manganese, see: (a) Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 7945−7952. (b) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759−2767.

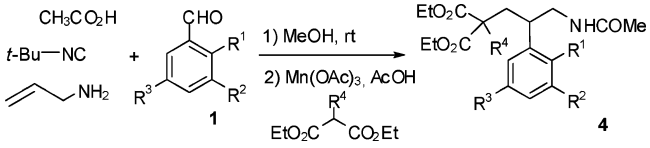
(10) For radical cyclization to indane, see: (a) Ly, T.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533−2536. (b) Kurono, N.; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Tetrahedron* **2004**, *60*, 1791−1801. (c) Bailey, W. F.; Mealy, M. J.; Wiberg, K. B. *Org. Lett.* **2002**, *4*, 791−794. (d) Kunding, E. P.; Ratni, H.; Crousse, B.; Bernardinelli, G. *J. Org. Chem.* **2001**, *66*, 1852−1860.

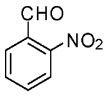
forms an Ugi adduct in quantitative yield, the following manganese treatment just gives a complex mixture (entry 7); *p*-methoxybenzaldehyde behaved similarly as well as pyridine carboxaldehyde **1g** (entry 8). The observed fragmentation does not seem to be limited to a specific isocyanide, and a small 7% decrease in yield was just observed when *tert*-butylisocyanide was replaced by cyclohexylisocyanide in the Ugi step (entry 1).

The main interest of this synthetic sequence lies in the complete rebuilding of the traditional Ugi adduct's framework with formation of indanes, a chemical family which has displayed significant biological activities (anti-HIV,[11] antihypertensive,[12] or thrombin inhibitor[12]).

The results obtained with aldehyde **1d** gives some clues into the mechanism involved in this transformation. To obtain indane **3d**, 6 equiv of manganese is needed. With 4.5 equiv of manganese acetate, the reaction gives the uncyclized malonate **4a** in good yield (Table 2). This latter was converted into **3d** when subsequently treated with Mn(III). When a substituted malonate is used, similar uncyclized products are obtained in good yields (Table 2, entries 2−4). This new formation of δ-amidomalonates represents in its own an interesting synthesis as easy malonate alkylation increases the diversity of the process and allows further transformations such as cyclization onto the amine or aromatic moiety.

Table 2. Formation of δ-Amidomalonates

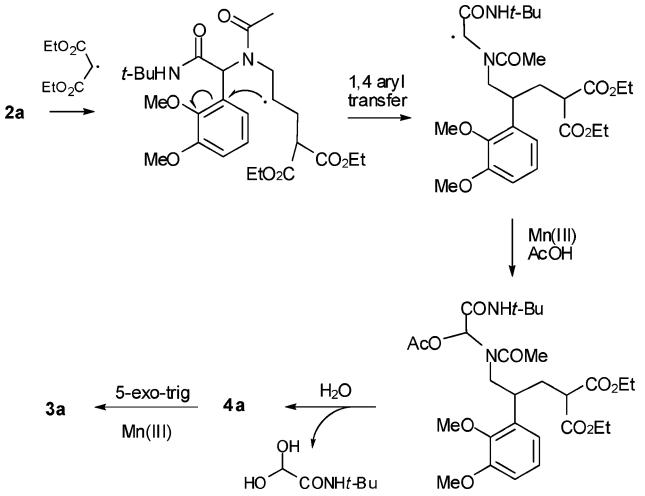


entry	starting aldehyde	R^4	time (h)	**4** (%)[a]
1	**1d**	H	4	**4a** (83)[b]
2	**1a**	Me	4	**4b** (71)
3	**1c**	Me	6	**4c** (70)
4	 **1h**	Me	8	**4d** (66)[c]

[a] The oxidation step was performed in acetic acid (90 °C, 0.3 M) with 3 equiv of malonate and 4.5 equiv of manganese acetate; the reaction was stopped after decoloration of the medium. [b] Four equivalents of malonate was used. [c] Six equivalents of manganese was used for completion.

All these results are in agreement with a 1,4-radical aryl migration as the key step of the transformation.[13] The peptidyl radical formed after rearrangement is oxidized and cleaved in acetic acid to give **4a** which cyclizes to **3a** under further oxidation with manganese acetate (Scheme 2).

Scheme 2. Proposed Mechanism for Indane Formation



In conclusion, we have shown that the Ugi reaction offers new entries for the obtention of indanes and δ-amidomalonate scaffolds by new manganese(III)-induced additions. Most noteworthy is the complete rebuilding of the traditional Ugi adduct's framework. The ability to assemble in a single step rather complex Ugi-type structures gives chemists unique opportunities to observe interesting couplings or cascades that might not settle easily on more simple adducts. Further work is in progress to explore the radical applications offered by these Ugi adducts.

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Supporting Information Available: Experimental procedures and spectral data for indanes and amidomalonates formed. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Molteni, V.; Rhodes, D.; Rubins, K.; Hansen, M.; Bushman, F. D.; Siegel, J. S. *J. Med. Chem.* **2000**, *43*, 2031−2039.
(12) Hanessian, S.; Ma, J. *Tetrahedron Lett.* **2001**, *42*, 8785−8788.
(13) For a review on radical aryl migrations, see: (a) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649−9667. (b) See also: Palframan, M. J.; Tchabanenko, K.; Robertson, J. *Tetrahedron Lett.* **2006**, *47*, 8423−8425.